UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: June 10, 2016

SUBJECT: **Diazinon** Draft Human Health Risk Assessment for Registration Review

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This document provides the HED's human health risk assessment for the Registration Review of Diazinon ([O,O-diethyl-O-(2-isopropyl-6-methy-4-pyrimidinyl)phosphorothioate].

1.0 Executive Summary

Diazinon is an organophosphate (OP) insecticide registered to control foliage and soil insects and pests on a variety of crops (primarily fruit, vegetables, and nuts) and on nursery stock ornamentals. Diazinon is currently formulated as soluble concentrate (SC) and wettable powder (WP) in water soluble packages (WSP) end-use products (EPs). There are also impregnated formulation products for use on cattle (ear tags). Application may be made via ground, chemigation, and aerial equipment, depending on crop. Maximum allowed application rates range from 0.5 lb ai/A to 4 lb ai/A.

Based on the registered use pattern for diazinon, humans may be exposed to diazinon in food as a result of direct application to crops and as a result of residues in commodities from livestock treated with ear tags. Diazinon, or its oxon metabolite (diazoxon), may also be consumed in drinking water since application to crops may result in diazinon reaching surface and ground water sources of drinking water. Dermal and inhalation exposures are anticipated for occupational handlers, as well as dermal exposures for post-application workers. There are currently no registered residential uses of diazinon; however, there is the potential for non-occupational exposure as a result of spray drift. This risk assessment considers all of the aforementioned exposure pathways.

U.S. tolerances are established for residues of diazinon on food commodities to support the registered uses. The residue of concern for tolerance enforcement is the parent compound diazinon. The potential residues of concern for risk assessment include diazinon and its cholinesterase inhibiting metabolites, hydroxydiazinon and diazoxon. Since hydroxydiazinon and diazoxon are typically not found on treated crops or in food commodities, and are not expected to occur on turf as a result of agricultural spray drift, they are not included in the dietary (food) or spray drift assessments. The residues of concern in drinking water are diazinon and diazoxon. Data on drinking water treatment suggest that in many water treatment facilities diazinon will degrade rapidly to the more toxic diazoxon. 100% conversion of diazinon to diazoxon in water is assumed for the dietary (drinking water) risk assessment.

Hazard Assessment

Diazinon is a member of the OP class of pesticides. Like other OPs, the initiating event in the adverse outcome pathway (AOP)/ mode of action (MOA) for diazinon involves inhibition of the enzyme acetylcholinesterase (AChE) via phosphorylation of the serine residue at the active site of the enzyme. This inhibition leads to accumulation of acetylcholine and ultimately to neurotoxicity in the central and/or peripheral nervous system. For diazinon, AChE inhibition (AChEI) is the most sensitive endpoint in the toxicology database in multiple species, durations, lifestages, and routes. Diazinon requires bioactivation to an oxon metabolite (diazoxon) to inhibit AChE. OPs also exhibit a phenomenon known as steady state AChEI. After repeated dosing at the same dose level, the degree of inhibition comes into equilibrium with the production of new, uninhibited enzyme. Therefore, steady state exposure assessments were conducted instead of the traditional repeated-dose scenarios.

The toxicology database for diazinon is adequate for risk assessment. Diazinon has high quality dose response data across multiple lifestages and durations via multiple routes for both red blood cell (RBC) and brain AChE inhibition. Clinical signs of neurotoxicity can be found throughout the database of toxicity studies at doses much higher than those causing inhibition of AChE.

Dermal and inhalation studies allow for route-specific evaluation. Cholinesterase data are also available for the oxon (comparative cholinesterase assays for adult and pup lifestages). For both diazinon and the oxon, diazoxon, RBC AChE was generally more sensitive than brain AChE; females were generally more sensitive than males; and PND11 pups were generally more sensitive than adults in the CCA studies. For diazinon, there was no indication of susceptibility of the fetus or pregnant female. No fetal or pregnant female data were available for diazoxon; however, the same qualitative toxicity profile is expected in the parent and the oxon (because of the bioactivation of the parent to the oxon). Therefore, the toxicology database for diazoxon is adequate for determining the relative toxicity of diazoxon to diazinon and for calculating toxicity adjustment factors for use in risk assessment. No additional data are required for diazoxon.

Diazinon is not likely to be carcinogenic in humans. In acute lethality studies, diazinon is Toxicity Category III for the oral, dermal, and inhalation routes. Diazinon is Toxicity Category III for eye and dermal irritation and is not a dermal sensitizer.

Endpoints and Uncertainty Factors for Risk Assessment

All endpoints for risk assessment were based on the most sensitive endpoint, RBC AChEI. All oral endpoints were derived from a high quality, well-conducted comparative cholinesterase assay (CCA) rat study (acute and repeated dosing), while dermal and inhalation endpoints were derived from route-specific studies. A point of departure (POD) for the acute dietary (all populations) exposure scenario is 3.0 mg/kg/day ($BMDL_{10}$). ((The $BMDL_{10}$ is the bench mark modeling dose (BMD) 95% lower confidence limit on a 10% response [ChEI])). For the steady state dietary and incidental oral exposure scenarios, the POD is 0.35 mg/kg/day ($BMDL_{10}$). For dermal steady state endpoints, the POD is 3.0 mg/kg/day (no adverse effect level, NOAEL). For inhalation steady state endpoints, the POD is 0.816 mg/m^3/day ($BMDL_{10}$)
The Food Quality Protection Act (FQPA) safety factor (SF; 10X) has been retained for infants, children, youth, and women of child-bearing age for all exposure scenarios due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see section 4.4). For all exposure scenarios, interspecies (10X) and intraspecies (10X) uncertainty factors were applied. As a result, a total uncertainty factor of 1000X was applied for all non-cancer exposure scenarios, except dietary exposures for the adult population subgroup 50-99 years old where the FQPA SF does not apply (total uncertainty factor = 100X).

Toxicity Adjustment Factors

The oxon metabolite of diazinon, diazoxon, has been found to be a more potent AChE inhibitor than diazinon. Diazoxon exposure may occur through drinking water. Therefore, to account for the increased potency of diazoxon, benchmark dose (BMD) modeling was used to evaluate relative toxicity and to estimate the toxicity adjustment factors (TAFs) for acute (12X) and steady state (9X) exposure durations.

Dietary (Food and Water) Exposure and Risk

Refined acute and steady state dietary (food and drinking water) exposure and risk assessments for diazinon were conducted using DEEM-FCID version 3.18 with 2003-2008 food consumption data from USDA's National Health and Nutrition Examination Survey, What We Eat in America (NHANES/WWEIA).

The highly refined dietary exposure assessments incorporated U. S. Department of Agriculture's Pesticide Data Program (USDA PDP) food monitoring data for diazinon, percent crop treated (PCT) data from the Biological and Economic Analysis Division (BEAD), and default or empirical processing factors. The Environmental Fate and Effects Division (EFED) provided estimated drinking water concentrations (EDWCs) for both low-end (cranberry) and high-end (melon and apple/pear) water scenarios. For the high-end scenarios, EFED provided daily time-series outputs that simulate 29 years of residues of diazinon in drinking water. The drinking water distributions assumed 100% conversion of diazinon to diazoxon and incorporated the acute and steady state TAFs.

The acute (food only) exposure estimates are not of concern (did not exceed 100% of the acute population adjusted dose (aPAD)) for the U.S. population and all population subgroups at the 99.9th percentile. Food exposures for children 1-2 years old, the most highly exposed population subgroup, utilized 15% of the aPAD. The acute exposure estimates for drinking water only (low- and high-end scenarios) for the most highly-exposed population subgroups (infants and children ages 1-2) exceed 100% of the aPAD at the 95th percentile of exposure (> 140% of the aPAD).

Since acute dietary exposures from drinking water alone were of concern for the highest exposed subpopulations (infants and children), drinking water exposures were not combined with exposures from food for these or any other population subgroups. Combining those exposures would result in even greater risk estimates of concern. The acute aggregate dietary (food and water) exposures and risk estimates are of concern.

The steady state dietary (food only) exposure estimates are not of concern (did not exceed 100% of the steady state population adjusted dose (ssPAD)) for the U.S. population and all population subgroups at the 99.9th percentile. Food exposures for children 1-2 years old, the most highly exposed population subgroup, utilized 100% of the ssPAD. The steady state exposure estimates for drinking water only (low- and high-end scenarios) for the most highly-exposed population subgroups (infants and children ages 1-2) exceed 100% of the ssPAD at the 95th percentile of exposure (> 1400% of the ssPAD).

Since dietary exposures from drinking water alone were of concern for the highest exposed subpopulations (infants and children), drinking water exposures were not combined with exposures from food. Combining those exposures would result in even greater risk estimates of concern. The steady state aggregate dietary (food and water) exposures and risk estimates are of concern.

Residential (Non-Occupational) Exposure and Risk

There are no residential uses of diazinon. All indoor and pet uses of diazinon were voluntarily cancelled effective November 15, 2001 (66 FR 5744) and all outdoor non-agricultural uses were voluntarily cancelled effective August 11, 2004 (69 FR 48864).

Aggregate Exposure and Risk

The acute aggregate dietary (food and water) exposures and risk estimates for the registered uses of diazinon are of concern. Because there are no residential uses for diazinon, the steady state aggregate assessment includes dietary (food and water) exposures only. The steady state

aggregate dietary (food and water) exposures and risk estimates for the registered uses of diazinon are of concern. Diazinon is classified as a "not likely to be carcinogenic to humans." Therefore, a quantitative cancer aggregate risk assessment is not required.

Non-Occupational Spray Drift Exposure and Risk

A quantitative non-occupational spray drift assessment was conducted for the registered agricultural uses of diazinon. Adult dermal and children's (1 to < 2 year old) dermal and incidental oral risk estimates from indirect exposure related to spray drift are of concern (i.e, Margins of exposure (MOEs) are all < 1000; Level of concern (LOC) =1000) at a range of distances (e.g., 0 to >300 feet) from the edge of the field depending on the spray-drift scenario. Results indicate that the major spray drift risk concerns are from aerial applications.

Volatilization/Residential Bystander

The Agency has developed a preliminary bystander volatilization inhalation exposure assessment for diazinon utilizing the currently available inhalation toxicity and air monitoring data. There are six air monitoring studies available for diazinon that were conducted at the request of California Department of Pesticide Regulation (CDPR). The comparison of the mean air concentration values against the steady state POD ($BMDL_{10}$ = 0.816 mg/m^3) is a reasonable match of the toxicological effect and exposure profile. This arithmetic mean comparison was completed to represent the potential for a seasonal exposure profile. The peak air concentration was also compared to the steady state POD and this is considered a conservative assessment of potential risk. For both single day and steady state exposure scenarios, there are risk estimates of concern for bystander volatilization inhalation (i.e., MOEs <1000; LOC=1000).

Occupational Handler Exposure

All occupational handler scenarios show risk estimates of concern with maximum feasible clothing and PPE [*i.e.*, a double layer of clothing, gloves and organic vapor respirator (PF10)] or engineering controls. The total combined (dermal + inhalation) occupational MOEs, assuming maximum PPE and/or engineering controls, ranged from 4 to 870 (LOC=1000).

Occupational Post-Application Exposure

There are chemical-specific dislodgeable foliar residue (DFR) studies available for diazinon. All occupational post-application risk estimates resulted in dermal MOEs of concern on day 0 with chemical-specific DFR inputs. The number of days for the MOE to reach the LOC of 1,000 ranges from 2 to 8 days for the registered uses of diazinon. Diazinon is classified as Toxicity Category III via the dermal route and for eye irritation and inhalation. It is not a skin sensitizer. Under 40 CFR 156.208 (c) (2), if the product contains only one active ingredient and is an organophosphate, the REI should be 48 hours, or 72 hours in areas where average rainfall is less than 25 inches per year. However, since steady state post-application risk estimates were a concern up until 8 days for some crop/activity combinations, the REI may need to be increased to address those concerns.

Based on the Agency's current practices, a quantitative non-cancer occupational post-application inhalation exposure assessment was not performed for diazinon at this time. If new policies or

procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for diazinon.

Human Studies Review

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include PHED 1.1; the AHETF database; the ARTF database; and the Residential SOPs (Turf SOP) are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[1].

2.0 HED Recommendations

2.1 Data Deficiencies

None.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical

The FDA PESTDATA database dated 1/94 (PAM, Vol. I, Appendix I) indicates diazinon is completely recovered using FDA Multiresidue Protocols D and E (PAM, Vol. I Sections 232.4 and 311.1/212.2). Diazoxon and hydroxydiazinon are also completely recovered using Protocol D.

Adequate analytical methodology is available for data collection and enforcing tolerances of diazinon. Ciba-Geigy Method AG-550 (along with modifications) is a GC/FPD method that adequately recovers diazinon, and its metabolites diazoxon and the hydroxy from plant and animal matrices.

2.2.2 International Harmonization

The residue definition for enforcement is the same for the U.S., Canada and Codex and includes parent compound diazinon. There are several commodities with U.S. tolerances that do not have Codex, Canada or Mexico maximum residue limits (MRLs) and, therefore, do not have any harmonization issues. Those include banana; blueberry; beet, garden, tops; cattle, fat; ginseng; hazelnut; rutabaga; sweet potato, roots; and watercress.

There are several commodities with U.S. tolerances for which there are either Codex MRLs, Canada MRLs, or both. Recommendations for harmonization were prioritized by Codex MRLs

[1] http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure

followed by Canadian MRLs. Where there exist Codex MRLs that are higher than the U.S. tolerances, it is recommended that the U.S. tolerances be increased to harmonize with Codex. Those commodities include almond, hulls; cherry, sweet; cherry, tart; onion, green; and plum, prune, fresh. Where there are no Codex MRLs, but the Canada MRLs are higher than U.S tolerances, it is recommended that the tolerances be increased to harmonize with Canada. Those include apricot; celery; endive; and nectarine. In cases where U.S. tolerances are higher than the Codex MRL (and can't be lowered because of potential over-tolerance residue concerns), but lower than the Canada MRL, it is recommended that those tolerances be increased to harmonize with Canada MRLs. Those cases include apple; lettuce; pear; spinach; strawberry; and vegetable, brassica, leafy, group 5. Finally, there are commodities where the current U.S. tolerance should not be altered because the U.S. level is higher than either the Codex MRL or the Canada MRL and cannot be lowered because of residue concerns, or because the U.S. level is already appropriately harmonized. Those commodities include almond; bean, lima; bean, snap, succulent; beet, garden, roots; caneberry subgroup 13-07A; carrot, roots; cucumber; cranberry; fig; kiwifruit; melon; onion, bulb; parsley, leaves; parsnip; pea, succulent; peach; pepper; pineapple; potato; radish; squash, summer; squash, winter; Swiss chard; tomato; turnip, roots; and turnip, tops.

The list of U.S. tolerances and international MRLs is in Appendix B. A summary of the established and HED-recommended tolerances for residues of diazinon can be found in Appendix C.

2.2.3 Recommended Tolerances

Permanent tolerances have been established in 40 CFR §180.153 for "residues of the pesticide diazinon O,O-diethyl O-[6-methyl-2-(1-methylethyl)-4-pyrimidinyl]phosphorothioate (CAS No. 333-41-5)" in or on various raw agricultural commodities ranging from 0.05 ppm to 3.0 ppm.

The tolerance expression for diazinon [40 CFR §180153(a) and 40 CFR §180.153(c)] has been reviewed and should be updated as follows based on HED's Interim Guidance on Tolerance Expressions (S. Knizner, 27-MAY-2009).

Tolerances are established for residues of the insecticide diazinon, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only diazinon (O,O-diethyl O-[6-methyl-2-(1-methylethyl)-4-pyrimidinyl]phosphorothioate) in or on the commodities.

A summary of the established and HED-recommended tolerances for residues of diazinon, based on harmonization, can be found in Appendix C.

2.3 Label Recommendations

No label recommendations have been identified. For occupational workers, a summary of the risk estimates has been provided and shows that there are risk estimates of concern for the registered uses of diazinon based on the label-required personal protective equipment (PPE; engineering controls) and restricted entry intervals (REIs). In addition, there are risk estimates of concern for adults and children resulting from spray drift from the currently registered agricultural uses of diazinon.

3.0 Introduction

3.1 Chemical Identity

Diazinon [O,O-diethyl-O-(2-isopropyl-6-methy-4-pyrimidinyl)phosphorothioate] is a nonsystemic insecticide used for the control of insects and pests on various fruits, vegetables, nuts and ornamentals. Diazinon is also used as a cattle ear tag treatment.

The nomenclature of diazinon and its metabolites, diazoxon (G-24567) and hydroxyl diazinon (CGA-14128), are summarized in Table 3.1.

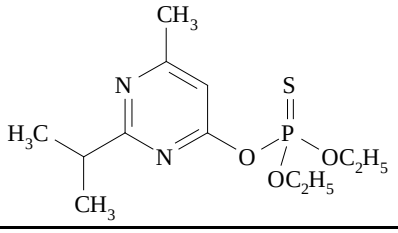
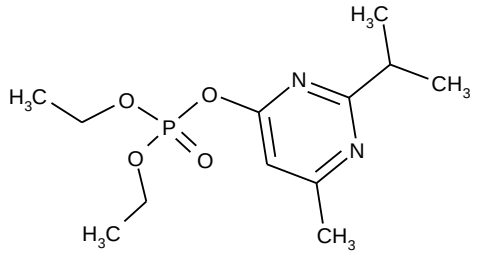
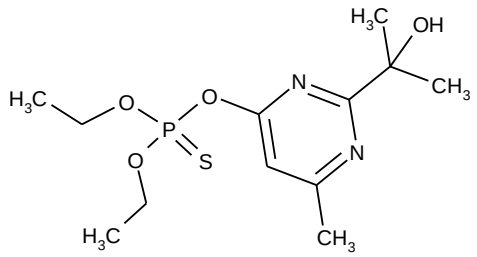
TABLE 3.1. Test Compound Nomenclature	
Parent Compound	Chemical Structure 
Common name	Diazinon
IUPAC name	Diethoxy-(6-methyl-2-propan-2-yl-pyrimidin-4-yl)oxy-sulfanylidene-phosphorane
CAS name	O,O-diethyl-O-(2-isopropyl-6-methyl-4-pyrimidinyl)phosphorothioate
CAS #	333-41-5
Metabolite	Chemical Structure 
Common name	Diazoxon (G-24567)
IUPAC name	-
CAS name	O,O-diethyl 6-methyl-2-(1-methylethyl)-4-pyrimidinyl phosphate
CAS #	962-58-3
Metabolite	Chemical Structure 

TABLE 3.1. Test Compound Nomenclature	
Common name	Hydroxyl Diazinon (CGA-14128)
IUPAC name	-
CAS name	O,O-diethyl O-(2-(1-hydroxy-1-methylethyl)-6-methyl-4-pyrimidinyl) phosphorothioate
CAS #	2814-20-2

3.2 Physical/Chemical Characteristics

Diazinon is a colorless to dark brown liquid. Diazinon is semi-volatile from dry non-sorbing surfaces, slightly volatile from water, and slightly volatile to non-volatile from moist soil and may be transported in air in both the vapor form and associated with particles (EFED, K. White, 6/1/2016, D418979). The breakdown rate in water is dependent on the acidity of water; breakdown is more rapid at highly acidic levels. Diazinon has a low persistence in soil and is considered moderately to slightly mobile.

The physiochemical properties of diazinon are summarized in Appendix D.

3.3 Pesticide Use Pattern

Diazinon is a nonsystemic OP insecticide/acaricide registered to control foliage and soil insects and pests on a variety of agricultural crops. Diazinon is currently formulated as soluble concentrate (SC) and wettable powder (WP) in water soluble packages (WSP) end-use products (EPs) containing between 48.2% and 50% ai. There are also impregnated formulation products for use on cattle (ear tags). The maximum single application rates for each crop or use site range from 0.5 to 4.0 lb ai/A. The registered labels permit application via ground equipment (airblast, groundboom and various hand held equipment), chemigation, and aerial equipment (lettuce only). A summary of registered labels and diazinon use directions are included in Appendix E.

3.4 Anticipated Exposure Pathways

Based on the registered use pattern for diazinon, humans may be exposed to diazinon in food as a result of direct application to crops and as a result of residues in commodities from animals treated with ear tags. Diazinon, or diazoxon, may also be consumed in drinking water since application to crops may result in diazinon reaching surface and ground water sources of drinking water. Dermal and inhalation diazinon exposures are anticipated for occupational handlers, as well as dermal exposures for post-application workers. There are currently no registered residential uses of diazinon; however, there is the potential for non-occupational exposure as a result of spray drift.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (http://www.archives.gov/federal-register/executive-orders/pdf/12898.pdf). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water

consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled from the U.S. Department of Agriculture's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

Diazinon is a member of the OP class of pesticides. Like other OPs, the initiating event in the adverse outcome pathway (AOP), also often called the mode of action (MOA), for diazinon involves inhibition of the enzyme acetylcholinesterase (AChE) via phosphorylation of the serine residue at the active site of the enzyme. This inhibition leads to accumulation of acetylcholine and ultimately to neurotoxicity in the central and/or peripheral nervous system (see Figure 1). Diazinon requires metabolic activation to the oxon metabolite to inhibit AChE. For diazinon, AChEI is the most sensitive endpoint in the toxicology database in multiple species, durations, lifestages, and routes. AChEI is the focus of this hazard characterization; the availability of reliable AChEI dose response data is one of the key determinants in evaluating the toxicology database.

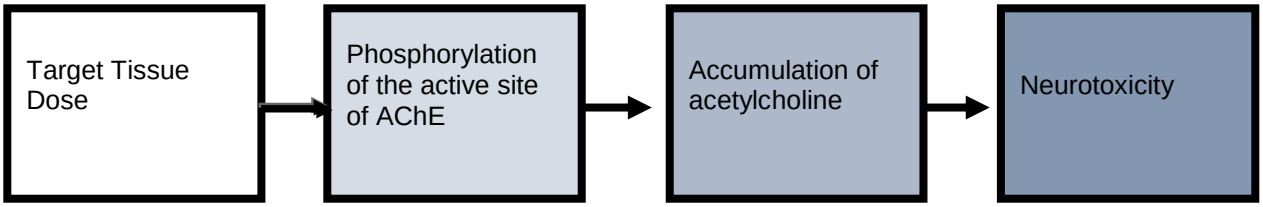


Figure 1. Adverse outcome pathway for OPs

4.1 Toxicology Studies Available for Analysis

The toxicology database for diazinon is adequate for risk assessment. Toxicology data requirements and confirmation that diazinon meets these requirements are presented in Appendix A.1. The database includes the following toxicity studies:

- Subchronic oral toxicity studies in rats, mice and dogs
- Chronic oral toxicity studies in rats and dogs
- Carcinogenicity studies in rats and mice
- Developmental studies in rats and rabbits
- Reproduction study in rats

- Acute and subchronic neurotoxicity studies in rats
- Developmental neurotoxicity (DNT) study in rats
- Comparative cholinesterase assay (CCA) study (repeated-dose and acute but not gestational)
- Delayed neurotoxicity study in hens
- Subchronic dermal toxicity study in rats
- Repeated-dosing inhalation study in rats
- Immunotoxicity study in mice
- Complete mutagenicity study battery
- Metabolism studies in rats

The gestational component of the CCA study was not submitted, but a DNT study provides an assessment of fetal and pregnant dam sensitivity; therefore, no additional gestational data are required at this time.

The toxicology database for diazoxon is adequate for the calculation of toxicity adjustment factors. The diazoxon database includes the comparative cholinesterase assay (CCA) study, which includes the repeated-dose and acute components for both adults and juveniles, but not the gestational component. Although no fetal or pregnant female AChE data were available for diazoxon, the same qualitative toxicity profile is expected for diazinon and diazoxon (bioactivation); therefore, no additional data are required at this time.

4.2 Absorption, Distribution, Metabolism, and Excretion (ADME)

Some OPs require metabolic activation (PON1 and CYP450) to the oxon metabolite, and this is the case with diazinon. A series of metabolism experiments were run with ^{14}C-labeled diazinon orally administered to Sprague-Dawley strain rats (MRID 41108901). Generally, absorption and distribution are rapid with extensive metabolism and no accumulation in the tissues. Excretion occurs almost exclusively by urine following a single dose or repeated doses in both sexes. Within 24 hours, most of the ^{14}C was recovered in the urine (58.2% in females and up to 93.3% in males) and smaller amounts (<2.5%) in the feces. After 7 days, regardless of sex, dose (10 or 100 mg/kg), or dosing regimen (single or repeated), recovery was 97-100%, with 87-95% in the urine, 2-3% in feces, and 1-2% of the label remained in the tissues. Tissue distribution revealed the highest residues in the erythrocytes. Three major metabolites were identified in the urine to indicate that diazinon is metabolized to liberate the pyrimidinyl group that is oxidized and excreted. Only trace amounts of parent diazinon were present in the urine or feces.

4.2.1 Dermal Absorption

Dermal absorption data were not submitted for diazinon. However, a dermal toxicity study was used for dermal exposure and risk assessments; therefore, a dermal absorption factor was not needed.

4.3 Toxicological Effects

Diazinon is an OP with a neurotoxic AOP; neurotoxicity is the most sensitive effect in all species, routes, and life stages and was used to derive points of departure. Diazinon has dose response data across multiple life stages, durations, and routes for both RBC and brain AChE

inhibition. Many of these studies have been evaluated using benchmark dose modeling techniques (see Appendix A.2 and Bever, 2015, D428865). Quality studies in the oral, dermal, and inhalation routes allow for route-specific evaluation. Based on the available data, diazinon causes dose-related inhibition in red blood cell (RBC) and brain AChE activity. Inhibition of RBC and brain AChE activity precedes clinical signs of AChEI and systemic toxicity.

As the effects of diazinon occur following bioactivation to its oxon form, diazoxon, the neurotoxic effects observed following administration of diazinon occur through diazoxon. A comparative cholinesterase assay with diazoxon resulted in cholinesterase inhibition at a dose 9-fold lower (repeated-dose studies) or 12-fold lower (acute studies) or more potent than with administration of the parent, diazinon (see Section 4.6.2).

The toxicity profile demonstrates that diazinon, like other organophosphate pesticides, has anti-cholinesterase activity in various species including hens, mice, rats, rabbits, and dogs. Clinical signs of neurotoxicity observed in laboratory animals following an acute (single) exposure are consistent with cholinesterase inhibition and include: tremors, convulsions, salivation, and dyspnea (labored breathing). Clinical signs of neurotoxicity can be found throughout the database of experimental toxicity studies at doses over 285-fold higher than those causing 10% inhibition of AChE. Inhibition of plasma, erythrocyte and/or brain cholinesterase activity occurs by all routes (oral, dermal, and inhalation) and for all durations of exposure. Diazinon did not result in organophosphate-induced delayed neuropathy (OPIDN) in hens. No histopathological lesions of the nervous system were seen in either the acute or subchronic neurotoxicity studies. In subchronic and chronic toxicity studies conducted in mice, rats and dogs, systemic toxicity was manifested as cholinergic signs; decreases in body weight and body weight gains.

For both diazinon and diazioxon, RBC AChE was generally more sensitive than brain AChE; females were generally more sensitive than males; and the PND11 pups were more sensitive than adults in the CCA study. For diazinon, there was no indication of susceptibility of the fetus or pregnant female. No fetal or pregnant female data were available for diazoxon; however, the same qualitative toxicity profile is expected in the parent and the oxon (because of the bioactivation of the parent to the oxon).

Prenatal developmental toxicity studies in rats and rabbits provided no evidence of increased susceptibility (based on AChEI) of fetuses following *in utero* exposure to diazinon. No developmental toxicity was seen at the highest doses tested. In the two-generation reproductive toxicity study, effects in the offspring (pup mortality) were observed; however, this effect was noted at a dose 19-fold higher than the POD, which is based on RBC AChEI, the most sensitive endpoint. Reproduction effects included decreased male and female mating and fertility indices and increased gestation length at 100-fold higher than the POD. Although AChEI was not measured in the developmental and reproduction studies, inhibition would have been expected at the doses tested. For OPs, there is also uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4).

Diazinon is not likely to be carcinogenic in humans. This weight of the evidence judgment is based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies and the lack of mutagenic activity.

Immunotoxicity was not observed in an immunotoxicity study in mice, where systemic effects (reduced body weights) were observed.

In acute toxicity testing, diazinon is Toxicity Category III for the oral, dermal, and inhalation routes. Diazinon is Toxicity Category III for eye and dermal irritation and is not a dermal sensitizer.

More detail concerning the characterization and quantification of the toxic effects of diazinon and diazoxon is provided in Appendices A.2. OPP's cholinesterase policy and use of BMD modeling is described. A table of the benchmark modeling results is provided in Appendix A.2 (Tables A.2.1 through A.2.7). A toxicity profile table can be found following the benchmark modeling table in Appendix A.2 (Tables A.2.8 and A.2.9). It is noted that the toxicity profile table has not been updated to include BMD results since these can be found in the previous tables (A.2.1 and A.2.2).

4.3.1 Critical Durations of Exposure

One of the key elements in risk assessment is the appropriate integration of temporality between the exposure and hazard assessments. One advantage of an AOP understanding is that human health risk assessments can be refined and focused on the most relevant durations of exposure. The following text provides an analysis of the temporal pattern of AChE inhibition from acute (single) and repeated dosing studies in laboratory animals for diazinon. This analysis provides the basis for determining which exposure durations are appropriate for assessing human health risk. Table 4.3.1.1 provides a summary of the results from experimental toxicology studies with diazinon for adult rats chosen to demonstrate the dosing duration-effect relationship. Data from the RBC AChEI are presented, because this compartment was the most sensitive to the effects of diazinon. Only the BMD_{10} results are shown, because the central estimate is used for purposes of comparison according to the BMD guidance.

Table 4.3.1.1. Diazinon BMD_{10} Results (mg/kg/day) for RBC AChE Inhibition Over Time in Adult Rats.

Days of Dosing	Males BMD_{10}	Females BMD_{10}	MRID#, Test
0.375 days (9 hours)	6.9	NF	43132203, Acute Time-Course for CCA [a]
0.375 days (9 hours)	4.1	1.8	43132204, Acute NT [a]
7	2.3	NF	46166302, Repeated Dose CCA [a]
15	-	0.1	45842602, Range Finder DNT [b]
87	3.4	0.2	40815003, Subchronic Oral [b]

[a] administered by gavage
[b] administered in the diet
BMD_{10} = estimated dose where AChE is inhibited by 10% compared to background.
NF = no model fit.

OPs exhibit a phenomenon known as steady state AChEI. After repeated dosing at the same dose level, the degree of inhibition comes into equilibrium with the production of new, uninhibited enzyme. At this point, the amount of AChEI at a given dose remains relatively consistent across duration. In general, OPs reach steady state within 2-3 weeks but this can vary among OPs. For diazinon, based on the available data and as presented in Table 4.3.1.1, time to achieve steady state is consistent with other OPs. Given the results in Table 4.3.1.1, single-day and steady state durations are appropriate for human health risk assessment. As such, the endpoint selection for diazinon focuses on acute, single-day effects and steady state effects.

Although the durations of the toxicity and exposure assessments may differ among the OPs, an exact match is not necessary and would suggest a level of precision that the toxicity data do not support. Given this, the 21-day and longer exposure assessment is scientifically supportable and also provides consistency with the OP cumulative risk assessment (OP Cumulative Risk Assessment (CRA); 2002, 2006) and across the single chemical risk assessment for the OPs. As such, the single chemical OP assessments will evaluate steady state (a 21-day assessment) instead of the typical chronic duration dietary assessment. The steady state point of departure is protective of any exposure duration longer than 21-days, including chronic exposure, since cholinesterase inhibition does not increase after reaching maximum inhibition or steady state.

4.4 Literature Review on Neurodevelopment Effects

For the OPs, historically the Agency has used inhibition of AChE as the POD for human health risk assessment; at present time, this policy continues. This science policy is based on decades of work which shows that AChE inhibition is the initial event in the pathway to acute cholinergic neurotoxicity. The use of AChE inhibition data for deriving PODs was supported by the FIFRA SAP (2008, 2012) for chlorpyrifos as the most robust source of dose-response data for extrapolating risk and is the source of data for PODs for diazinon. A detailed review of the epidemiological studies used in this review can be found either in the 2014 chlorpyrifos revised draft human health risk assessment (D424485, D. Drew et al., 12/29/2014) or in the 2015 literature review for other organophosphates (OPP/USEPA; D331251; 9/15/15).

Newer lines of research on OPs in the areas of potential AOPs, *in vivo* animal studies, and notably epidemiological studies in mothers and children, have raised some uncertainty about the Agency's risk assessment approach with regard to the potential for neurodevelopmental effects in fetuses and children. Many of these studies have been the subject of review by the agency over the last several years as part of efforts to develop a risk assessment for chlorpyrifos (D424485, D. Drew et al., 12/29/2014). Initially, the Agency focused on studies from three US cohorts: 1) The Mothers and Newborn Study of North Manhattan and South Bronx performed by the Columbia Children's Center for Environmental Health (CCCEH) at Columbia University; 2) the Mt. Sinai Inner-City Toxicants, Child Growth and Development Study or the "Mt. Sinai Child Growth and Development Study;" and 3) the Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS) conducted by researchers at University of California Berkeley. The agency has evaluated these studies and sought external peer review (FIFRA SAP reviews in 2008 and 2012; federal panel, 2013[2]) and concludes they are of high quality. In the three US epidemiology cohort studies, mother-infant pairs were recruited for the purpose of studying the potential health effects of environmental exposures during pregnancy on subsequent child development. Each of these cohorts evaluated the association between prenatal chlorpyrifos and/or OP exposure (with adverse neurodevelopmental outcomes in children through age 7 years. For the 2014 chlorpyrifos revised human health risk assessment (D424485, D. Drew et al., 12/29/2014), EPA included epidemiologic research results from these three US prospective birth cohort studies but primarily focused on the results of CCCEH since this cohort has published studies on the association between cord blood levels of chlorpyrifos and neurodevelopmental outcomes. The agency retained the FQPA 10X Safety Factor (SF) in the 2014 chlorpyrifos revised risk assessment, in large part, based on the findings of these studies.

[2] http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0170

In the 2015 updated literature review (OPP/USEPA; D331251; 9/15/15), the agency conducted a systematic review expanding the scope of the 2012/2014 review focused on US cohort studies with particular emphasis on chlorpyrifos. The expanded 2015 review includes consideration of the epidemiological data on any OP pesticide, study designs beyond prospective cohort studies, and non-U.S. based studies. The updated literature review identified seven studies which were relevant (Bouchard et al., 2010; Fortenberry et al., 2014; Furlong et al., 2014; Guodong et al., 2012; Oulhote and Bouchard, 2013; Zhang et al., 2014; Shelton et al., 2014). These seven studies have been evaluated in context with studies from the 2012/2014 review (D424485, D. Drew et al., 12/29/2014). Only a brief summary is provided below.

The OP exposure being assessed in many of these studies used concentrations of urinary dialkyl phosphate metabolites (DAPs) as the urinary biomarker. Total DAPs is a non-specific measure of OP exposure and is the sum of six separate molecules - three dimethyl alkylphosphate (DMAP) molecules of DMP, DMTP, DMDTP, and three diethyl alkylphosphate (DEAP) molecules of DEP, DETP, and DEDTP. Each metabolite is a breakdown product from multiple OPs (Table 4.4.-1; CDC, 2008)[3]. Specifically, DMP, DMTP, and DMDTP are associated with 18, 13, and 5 OPs, whereas DEP, DETP, and DEDTP are associated with 10, 10, and 4 OPs, respectively. Thus, using urinary DAPs alone as an exposure measure, it is not possible to separate the exposure and associated effects for single, specific OPs.

Table 4.4.1. CDC Table of organophosphate pesticides and their dialkyl phosphate metabolites (2008).

Pesticide	DMP	DMTP	DMDTP	DEP	DETP	DEDTP
Azinphos methyl	X	X	X			
Chlorethoxyphos				X	X	
Chlorpyrifos				X	X	
Chlorpyrifos methyl	X	X				
Coumaphos				X	X	
Dichlorvos (DDVP)	X					
Diazinon				X	X	
Dicrotophos	X					
Dimethoate	X	X	X			
Disulfoton				X	X	X
Ethion				X	X	X
Fenitrothion	X	X				
Fenthion	X	X				
Isazaphos-methyl	X	X				
Malathion	X	X	X			
Methidathion	X	X	X			
Methyl parathion	X	X				
Naled	X					
Oxydemeton-methyl	X	X				
Parathion				X	X	
Phorate				X	X	X
Phosmet	X	X	X			

[3] http://www.cdc.gov/nchs/data/nhanes/nhanes_03_04/l26opd_c_met_organophosphorus_pesticides.pdf

Table 4.4.1. CDC Table of organophosphate pesticides and their dialkyl phosphate metabolites (2008).						
Pesticide	DMP	DMTP	DMDTP	DEP	DETP	DEDTP
Pirimiphos-methyl	X	X				
Sulfotepp				X	X	
Temephos	X	X				
Terbufos				X	X	X
Tetrachlorviphos	X					
Trichlorfon	X					

DMP = dimethylphosphate; DEP = diethylphosphate; DMTP = dimethylthiophosphate; DMDTP = dimethyldithiophosphate; DETP = diethylthiophosphate; DEDTP = diethyldithiophosphate.

For studies which measured urinary 3,5,6-trichloro-2-pyridinol (TCPy) (e.g., Fortenberry et al., 2014; Eskenazi et al., 2007; Whyatt et al., 2009), this metabolite can be derived from chlorpyrifos, chlorpyrifos-methyl, and the herbicide triclopyr. TCPy is also the primary environmental degradate of chlorpyrifos, chlorpyrifos-methyl, and triclopyr; thus exposure can be found directly on food treated with these pesticides. CCCEH studies have largely used chlorpyrifos measured in cord blood as the specific biomarker (e.g., Lovasi et al., 2010; Whyatt et al., 2004; Rauh et al., 2011). The CHARGE study (Shelton et al., 2015) did not measure biomarkers but instead used geospatial analysis to focus on the residential proximity to OP exposure using data from the California Department of Pesticide Regulation, with five OPs accounting for a total of 73% of the pesticide applied near residential settings (chlorpyrifos, acephate, diazinon, bensulide, and dimethoate).

Similarly, DAPs can be found directly on food following OP applications (Zhang et al., 2008; Chen et al., 2012). Specifically, studies have shown that DAPs may form as environmental degradates from abiotic hydrolysis, photolysis, and plant metabolism (Zhang et al., 2008; Chen et al., 2012; Racke et al., 1994). Furthermore, since these DAPs are excreted more rapidly and extensively than the parent OPs (Zhang et al., 2008; Forsberg et al., 2008), direct exposure to DAPs may lead to an overestimate of OP exposure when using urinary DAPs as a biomarker of OP exposure. The agency recognizes that this is a source of uncertainty when using DAPs for assessing OP exposure and will continue to monitor this issue in future assessments.

With respect to neurological effects near birth, the CHAMACOS and Mt. Sinai cohorts measured neurological effects at birth, and observed a putative association with total DEAP, total DMAP, and total DAP exposure (Engel et al., 2007; Young et al., 2005). Similarly, a Chinese study (Zhang et al., 2014) reported statistically significant associations for total DEAPs, total DMAPs, and total DAPs from prenatal OP pesticide exposure and neonatal neurodevelopment assessed 3 days after birth. However, another cross-sectional Chinese study, Guodong et al. (2012), observed no association with urinary DAPs and a developmental quotient score for 23-25 month old children.

The 3 US cohorts (CCCEH, Mt. Sinai, CHAMACOS) each reported evidence of impaired mental and psychomotor development, albeit not consistent by age at time of testing (ranging from 6 month to 36 months across the three cohorts). Attentional problems and ADHD were reported by three prospective cohorts [Rauh et al., 2006; Eskenazi et al., 2007; Marks et al., 2010; and Fortenberry et al. (2014)] investigators with additional support from a case control study, Bouchard et al. (2010). The exposure metric varied among these studies. Specifically,

Fortenberry et al. (2014) found suggestive evidence of an association with TCPy and ADHD in boys, whereas statistically significant associations were observed by Rauh et al. (2006) with chlorpyrifos exposure and ADHD. Eskenazi et al. (2007) reported associations with total DMAPs and total DAPs and ADHD; Marks et al. (2010) reported associations with total DEAP, DMAP, and total DAP exposure and ADHD. In a national cross-sectional study of Canadian children, using 2007-2009 data for children age 6-11 years (Oulhote and Bouchard, 2013), there were no overall statistically significant associations observed between child urinary DEAP, DMAP, or total DAP metabolite levels and parentally reported behavioral problems. In contrast, Bouchard et al. (2010), looking at U.S. children age 8-15 years in the 2000-2004 National Health and Nutrition Examination Survey (NHANES), observed a positive association between attention and behavior problems and total DAPs and DMAPs, but not DEAPs. As part of their analysis, Oulhote and Bouchard (2013) noted that their outcome assessment for behavioral problems may not have been as sensitive as Bouchard et al. (2010), which may in part account for the difference in the observed results from these studies.

In addition, the three US cohorts and the CHARGE study have reported suggestive or positive associations between OP exposure and autism spectrum disorders (Rauh et al., 2006; Shelton et al., 2014; Eskenazi et al., 2007; Furlong et al., 2014). Specifically, Furlong et al. (2014) documented suggestive evidence of an association between total DEAP exposure and reciprocal social responsiveness among blacks and boys. Eskenazi et al. (2007) reported a statistically significant association between pervasive developmental disorder (PDD) and total DAP exposure, whereas Eskenazi et al. (2010) reported non-significant, but suggestive, increased odds of PDD of 2.0 (0.8 to 5.1; p=0.14). Rauh et al. (2006) documented a significant association between PDD and specifically chlorpyrifos exposure. Both PDD and reciprocal social responsiveness are related to the autism spectrum disorder. Using a different exposure assessment method (geospatial analysis and residential proximity to total OP exposure), Shelton et al. (2014) also showed statistically significant associations between total OP exposure and ASD. While these studies vary in the magnitude of the overall strength of association, they have consistently observed a positive association between OP exposure and ASD. Finally, CCCEH, Mt. Sinai, CHAMACOS have reported an inverse relation between the respective prenatal measures of chlorpyrifos and intelligence measures at age 7 years (Rauh et al., 2011; Engel et al., 2011; Bouchard et al., 2011).

Across the epidemiology database of studies, the maternal urine, cord blood, and other (meconium) measures provide evidence that exposure did occur to the fetus during gestation but the actual level of such exposure during the critical window(s) of susceptibility is not known. While significant uncertainties remain about the actual exposure levels experienced by mothers and infant participants in the children's health cohorts, it is unlikely that these exposures resulted in AChE inhibition. As part of the CHAMACOS study, Eskenazi et al. (2004) measured AChE activity and showed that no differences in AChE activity were observed. The biomarker data (chlorpyrifos) from the Columbia University studies are supported by the agency's dose reconstruction analysis using the PBPK-PD model (D424485, D. Drew et al., 12/29/2014). Following the recommendation of the FIFRA SAP (2012), the agency conducted a dose reconstruction analysis of residential uses available prior to 2000 for pregnant women and young children inside the home. The PBPK-PD model results indicate for the highest exposure considered (i.e., indoor broadcast use of a 1% chlorpyrifos formulation) <1% RBC AChE inhibition was produced in pregnant women. While uncertainty exists as to actual OP exposure at (unknown) critical windows of exposure, EPA believes it is unlikely individuals in the epidemiology studies experienced RBC AChE inhibition.

A review of the scientific literature on potential modes of action/adverse outcome pathways (MOA/AOP)[4] leading to effects on the developing brain was conducted for the 2012 FIFRA SAP meeting (USEPA, 2012) and updated for the December 2014 chlorpyrifos revised risk assessment (D424485, D. Drew et al., 12/29/2014). In short, multiple biologically plausible hypotheses and pathways are being pursued by researchers that include targets other than AChE inhibition, including cholinergic and non-cholinergic systems, signaling pathways, proteins, and others. However, no one pathway has sufficient data to be considered more credible than the others. The fact that there are, however, sparse AOP data to support the *in vitro* to *in vivo* extrapolation, or the extrapolation from biological perturbation to adverse consequence significantly limits their quantitative use in risk assessment. The SAP concurred with the agency in 2008 and 2012 about the lack of definable key events in a MOA/AOP leading to developmental neurobehavioral effects. However, since the 2014 literature review, there are no substantive changes in the ability to define and quantitate steps in an MOA/AOP leading from exposure to effects on the developing brain. Published and submitted guideline DNT laboratory animal studies have been reviewed for OPs as part of the 2012/2014 review (D424485, D. Drew et al., 12/29/2014) and the updated 2015 review (OPP/USEPA; D331251; 9/15/15). Neurobehavioral alterations in laboratory animals were often reported, albeit at AChE inhibiting doses, but there was generally a lack of consistency in terms of pattern, timing, or dose-response for these effects, and a number of studies were of lower quality. However, this information does provide evidence of long-lasting neurodevelopmental disorders in rats and mice following gestational exposure.

At this time, a MOA(s)/AOP(s) has/have not been established for neurodevelopmental outcomes. This growing body of literature does demonstrate, however, that OPs are biologically active on a number of processes that affect the developing brain. Moreover, there is a large body of *in vivo* laboratory studies which show long-term behavioral effects from early life exposure, albeit at doses which cause AChE inhibition. EPA considers the results of the toxicological studies relevant to the human population, as qualitatively supported by the results of epidemiology studies. The agency acknowledges the lack of established MOA/AOP pathway and uncertainties associated with the lack of ability to make strong causal linkages and unknown window(s) of susceptibility. These uncertainties do not undermine or reduce the confidence in the findings of the epidemiology studies. The epidemiology studies reviewed in the 2012/2014 and 2015 literature reviews represent different investigators, locations, points in time, exposure assessment procedures, and outcome measurements. Despite all these differences in study design, with the exception of two negative studies in the 2015 literature review (Guodong et al., 2012; Oulhote and Bouchard, 2013), authors have identified associations with neurodevelopmental outcomes associated with OP exposure across four cohorts and twelve study citations. Specifically, there is evidence of delays in mental development in infants (24-36 months), attention problems and autism spectrum disorder in early childhood, and intelligence decrements in school age children who were exposed to OPs during gestation. Investigators reported strong measures of statistical association across several of these evaluations (odds ratios 2-4 fold increased in some instances), and observed evidence of exposures-response trends in some instances, *e.g.*, intelligence measures.

[4] Mode of action (MOA) and adverse outcome pathways (AOPs) describe a set of measureable key events that make up the biological processes leading to an adverse outcome and the causal linkages between such events.

As section 408(b)(2)(C) of the FFDCA instructs EPA, in making its "reasonable certainty of no harm" finding, that in "the case of threshold effects, an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children." Section 408 (b)(2)(C) further states that "the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children." Given the totality of the evidence, there is sufficient uncertainty in the human dose-response relationship for neurodevelopmental effects which prevents the agency from reducing or removing the statutory 10X FQPA Safety Factor. For the diazinon DRA, a value of 10X has been applied. Similarly, a database uncertainty factor of 10X will be retained for occupational risk assessments. The agency will continue to evaluate the epidemiology studies and pursue approaches for quantitative or semi-quantitative comparisons between doses which elicit AChE inhibition and those which are associated with neurodevelopmental outcomes prior to a revised human health risk assessment.

4.5 Safety Factor for Infants and Children (FQPA SF)

As noted above, the lack of an established MOA/AOP for neurodevelopmental effects makes quantitative use of the epidemiology studies in risk assessment challenging, particularly with respect to determining dose-response, critical duration of exposure, and window(s) of susceptibility. However, exposure levels in the range measured in the epidemiology studies are likely low enough that they are unlikely to result in AChE inhibition. Epidemiology studies consistently identified associations with neurodevelopmental outcomes associated with OP exposure such as delays in mental development in infants (24-36 months), attention problems and autism spectrum disorder in early childhood, and intelligence decrements in school age children. Therefore, there is a need to protect children from exposures that may cause these effects; this need prevents the Agency from reducing or removing the statutory FQPA Safety Factor[5]. **Thus, the FQPA 10X Safety Factor will be retained for diazinon for the population subgroups that include infants, children, youth, and women of childbearing age for all exposure scenarios.**

4.5.1 Completeness of the Toxicology Database

The database of toxicology studies for diazinon is complete and includes developmental studies in rat and rabbit, a reproductive toxicity study, a DNT, and a comparative ChE study with acute and repeated dose components for adults and juveniles. Although the gestational component of the CCA was not conducted, the DNT study provides AChE data for both the fetus and pregnant dam to evaluate potential lifestage sensitivity.

For diazoxon, a CCA study with acute and repeated dose components for both adults and juveniles is available. No fetal or pregnant female data were available for diazoxon; however, the same qualitative toxicity profile is expected in the parent and the oxon (because of the bioactivation of the parent to the oxon).

[5] OPP's standard approaches are consistent with EPA's children's environmental health policy. https://www.epa.gov/children/epas-policy-evaluating-risk-children

4.5.2 Evidence of Neurotoxicity

Diazinon and its oxon, diazoxon, are OPs with a neurotoxic AOP; neurotoxicity is the most sensitive effect in all species, routes, and lifestages and is being used to derive PODs for risk assessment. Therefore, the risk assessment is protective of potential neurotoxicity for all life stages and routes of exposure.

4.5.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

Prenatal developmental toxicity studies in rats and rabbits provided no evidence of increased susceptibility (based on ChEI) of rat or rabbit fetuses following *in utero* exposure to diazinon. Although there appears to be sensitivity in the reproduction study, the effect in the young occurred at high doses and cholinesterase measurements were not performed. Cholinesterase inhibition is expected at significantly lower doses than those doses causing the pup effects in the reproduction study. As a result, if cholinesterase measurements had been included in the reproduction study, significant inhibition would have been expected in both parental and juvenile rats. Therefore, there is no concern for potential offspring sensitivity from the reproduction study since selected endpoints are based on cholinesterase inhibition.

As discussed in Section 4.4, there is uncertainty in the human dose-response relationship for neurodevelopmental effects and this warrants retention of the FQPA Safety Factor for the population subgroups that include infants, children, youth, and women of childbearing age for all exposure scenarios.

4.5.4 Residual Uncertainty in the Exposure Database

There is no residual uncertainty in the exposure database. Dietary risk estimates were based on refined estimates of residues in foods and estimates of the percentage of the crop that may be treated. In addition, for drinking water, upper-bound water concentration estimates based on modeling were assumed. The dietary exposure estimates are not underestimated. There are currently no registered residential uses.

4.6 Toxicity Endpoint and Point of Departure Selections

4.6.1 Dose-Response Assessment

Table 4.6.4.1 summarizes the diazinon toxicity endpoints and PODs selected from an evaluation of the database. This endpoint selection was based on a weight of the evidence evaluation using the following considerations:

- *Relative sensitivity of the brain and RBC compartments*: The RBC AChE data were more sensitive than the brain AChE data to diazinon and diazoxon across most studies, durations, lifestages, and routes. As such, OPP has relied upon the RBC AChE data in POD derivation.
- *Potentially susceptible populations (fetuses, juveniles, pregnancy, or sex*): The available AChE data across lifestages (adults and juveniles) suggest that pups are more sensitive than the adult at doses selected for risk assessment. AChE data for the gestational component of the CCA study are not available; however, BMD results from the DNT study did not suggest fetal susceptibility nor susceptibility of the pregnant female when

compared to other repeated dose studies. Females were generally more sensitive than males and therefore relied upon for endpoints. See Appendix A.5 for information concerning sex and lifestage sensitivity.

- *Route of exposure:* It is preferred to match, to the degree possible, the route of exposure in the toxicity study with that of the exposure scenario(s) of interest. In the case of diazinon, there are oral, dermal, and inhalation studies, which contain quality dose-response AChEI data. Only oral route data (CCA study) are available for the oxon.
- *Duration of exposure:* It is preferred to match, to the degree possible, the duration of toxicity study with that of the exposure duration of interest. In the case of diazinon, there are single day and repeat dose oral studies and repeat dose dermal and inhalation studies. In the case of the oxon, there are single day and repeat dose oral studies.
- *Consistency across studies:* In cases where multiple datasets are available for a single duration, it is important to evaluate the extent to which data are consistent (or not) across studies. Diazinon and diazoxon consistently demonstrated AChEI for the RBC compartment, however the BMDs did vary study to study as the BMDs were influenced by large dose spreads within studies as well as by the variability of AChEI within the study dose groups. However, considering that different labs conducted the studies across several years, the diazinon database demonstrated adequate consistency in RBC AChEI.

Descriptions of the primary toxicity studies used for selecting toxicity endpoints and PODs for various exposure scenarios are presented in Appendix A of this document. Summary tables of BMD analyses can also be found in Appendix A, and the technical details of the analysis can be found in the BMD memo (Bever, 2015; TXR # 0057257).

Consistent with risk assessments for other AChE-inhibiting compounds, OPP has used a benchmark response (BMR) level of 10% and has thus calculated for each scenario a BMD_{10} and a $BMDL_{10}$. The BMD_{10} is the estimated dose where ChE is inhibited by 10% compared to background. The $BMDL_{10}$ is the lower confidence bound on the BMD_{10}. As a matter of science policy, the Agency uses the BMDL, not the BMD, for use as the POD (USEPA, 2012). All BMD/BMDL modeling for all individual datasets was completed using USEPA BMD Software, version 2.2; an exponential model was used to fit the data. BMD results from the OP Cumulative Risk Assessment ((CRA (2002, 2006)) were included in the endpoint selection weight of evidence evaluation. In studies where results are not listed, in general poor dose spacing in the studies prevented accurate BMD and BMDL values to be derived, since the data could not be reliably fit. Although these data sets could not be accurately modeled, the LOAELs from the studies were considered as part of the weight of evidence in selecting endpoints.

Acute Dietary Endpoint (All Populations)

A POD for the acute dietary (all populations) exposure scenario was derived from the acute response observed in the acute CCA rat study (MRID 46166301). A $BMDL_{10}$ of 3.0 mg/kg was selected and was associated with RBC AChE inhibition in female pups (PND 11). The corresponding BMD_{10} was 3.4 mg/kg. RBC cholinesterase inhibition was selected as the endpoint for the acute POD, since BMD_{10} values were lower than those for brain cholinesterase inhibition. Data from the PND 11 pups are appropriate for acute POD derivation, since effects were observed after a single exposure, and pups were the more sensitive life stage. The study was also selected because it had the best dose response and curve fit of the various acute studies available (listed in Appendix A, Table 2.1).

An uncertainty factor of 1000X ((10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for FQPA safety factor due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4)) is applied to the $BMDL_{10}$ to obtain an aPAD of 0.003 mg/kg for all exposure scenarios, except adults 50-99. Excluding the FQPA SF for adults 50-99, the aPAD is 0.03 mg/kg/day.

Steady State Dietary Endpoint (All Populations)
A POD for the steady state dietary (all populations) exposure scenario was derived from the repeated-dose response observed in a CCA rat study (MRID 46166302). A $BMDL_{10}$ of 0.35 mg/kg/day was selected and was associated with RBC AChE inhibition in female pups (PND 11 initially). The corresponding BMD_{10} was 0.52 mg/kg/day. RBC cholinesterase inhibition was selected as the endpoint for the POD, since BMD_{10} values were lower than those for brain cholinesterase inhibition. Of the best modeled data sets, data from the PND 11 pups provided the most sensitive response; therefore, it was protective of all lifestages. For diazinon, data suggests that steady state was obtained for both males and females before day 21. The CCA study was also selected because it had the best dose response curve and fit of the various repeat-dose studies available (listed in Appendix A Table 2.1) and used 5 dose groups instead of the typical 4.

An uncertainty factor of 1000X ((10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for FQPA safety factor due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4)) is applied to the $BMDL_{10}$ to obtain an ssPAD of 0.00035 mg/kg/day for all exposure scenarios, except adults 50-99. Excluding the FQPA SF for adults 50-99, the ssPAD is 0.0035 mg/kg/day.

Incidental Oral Endpoint, Steady State
A POD of 0.35 mg/kg/day was selected due to the same rationale provided above for the steady state dietary endpoint. A total uncertainty factor of 1000X ((10X for interspecies extrapolation, 10X for intraspecies variation, and 10X for FQPA safety factor due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4)) is appropriate, allowing a Level of Concern (LOC) of 1000.

Dermal Endpoints, Steady State
A steady state dermal POD was selected from a route-specific rat 90-day dermal toxicity study (MRID 48497201) based on brain and RBC AChE inhibition (NOAEL = 3.0 mg/kg/day; LOAEL = 10.0 mg/kg/day) in the adult female rat. Results from the females are protective of the males in this study since inhibition in males was not observed at 10 mg/kg/day. The female brain and RBC AChE data were used for BMD analysis, however the data resulted in poor curve fits and therefore the traditional NOAEL/LOAEL approach was used for risk assessment. Although adult female data are relied upon for the dermal assessment, the retention of the 10X FQPA factor along with the 10X intraspecies and 10X interspecies factors is protective of all lifestages, including pups. This route-specific study is appropriate for the route and duration of exposure. The LOC is 1000.

Inhalation Endpoints, Steady State
A steady state inhalation POD was selected from a route-specific 21-day inhalation toxicity study (MRID 41557402) in adult female rats based on RBC AChE inhibition ($BMDL_{10}$ = 0.816 mg/m^3/day; BMD_{10} = 0.988 mg/m^3/day). The inhalation AChE data suggest that the female AChEI data are protective of the male AChEI data in this study. Concern for pregnant female

workers is low since the oral AChEI data suggest pregnant female is not more sensitive than non-pregnant females, as evaluated in the inhalation study. Diazinon has a relatively high vapor pressure, and the particle size distribution from this study indicates that most particles were well below the respirable range for an aerosol (0.7-1.4 µm), suggesting that the exposure was mainly via a vapor. A human equivalent concentration (HEC) was not generated from this study based on the following conditions: 1) high vapor pressure of diazinon (other organophosphates, such as dicrotophos and terbufos, with similar vapor pressures were primarily vapor); 2) lack of data indicating what percentage was vapor versus particles; 3) the geometric standard deviations were greater than the mass median aerodynamic diameters; and 4) the effects observed were only systemic (AChE inhibition) without portal of entry effects (e.g., irritation). Instead, the concentration was adjusted to consider the exposure in the rat study (exposed for 6 hours on each of 5 days per week) to anticipated worker exposure (exposed 8 hours on each of 5 days per week). A conversion factor of 44 L/h*kg was applied and the value multiplied by the anticipated 8 hour exposure period to obtain the mg/kg/day value, 0.22 mg/kg/day. A total uncertainty factor of 1000X is appropriate (10X for interspecies extrapolation, 10X for intraspecies variation, and 10X FQPA/database uncertainty factor), allowing a LOC of 1000.

4.6.2 Toxicity Adjustment Factors for Diazoxon

Toxicity adjustment factors (TAFs) are used to aggregate the concentrations of the parent and the more toxic metabolite (diazoxon). The toxicity of diazoxon is compared to the toxicity of diazinon using the BMD_{10} when quality data sets are amenable to BMD modeling. Multiplying the measured diazoxon residues by the TAF provides a measure of diazinon-equivalents. Toxicity data for diazoxon through the dermal and inhalation routes of exposure are not available; therefore, the oral TAF will be used for all routes of diazoxon exposure. **The oxon form was a more potent inhibitor of RBC AChE than the diazinon parent by a factor of 12X in the acute studies and 9X in the repeat-dose studies.** The TAFs are provided in the following table.

Route of Administration	Diazoxon BMD_{10} (mg/kg/day)	Diazinon BMD_{10} (mg/kg/day)	Toxicity Adjustment Factor [a]
Acute Oral (pups)	0.275 [b]	3.362	12
Steady State Oral (adults)	0.260	2.339 [c]	9

[a] Values were obtained by dividing the diazinon BMD_{10} by the diazoxon BMD_{10}. Multiplying the measured diazoxon residues by the toxicity adjustment factor provides a measure of diazinon-equivalents.
[b] Values were obtained from female pup RBC AChEI BMD_{10}s from MRIDs 46166301 (diazinon) and 48663504 (diazoxon).
[c] Values were obtained from male adult RBC AChEI BMD_{10}s from MRIDs 46166302 (diazinon) and 48663505 (diazoxon).

Exposure scenarios are acute and steady state dietary, steady state incidental oral (spray drift), steady state dermal, and steady state inhalation.

4.6.2 Recommendation for Combining Routes of Exposures for Risk Assessment

When there are potential occupational and residential exposures to a pesticide, the risk assessment must address exposures from three major routes (oral, dermal, and inhalation) and determine whether the individual exposures can be combined if they have the same toxicological effects. PODs for the incidental oral, dermal, and inhalation routes are all derived from RBC AChE inhibition. As a result, exposure from all routes can be combined.

4.6.3 Cancer Classification and Risk Assessment Recommendation

Diazinon is classified as a "not likely to be carcinogenic to humans," based on the lack of evidence of carcinogenicity in mice and rats when tested at doses that were adequate to assess the carcinogenic potential of this organophosphate. Furthermore, diazinon was shown to be non-mutagenic following both *in vivo* and *in vitro* mutagenicity assays.

4.6.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.6.4.1 Summary of Toxicological Doses and Endpoints and Points of Departure for Diazinon in Dietary and Non-Occupational Human Health Risk Assessments [a]

Exposure Scenario	Point of Departure (mg/kg/day)	Uncertainty/FQPA Factors	RFD, PAD, & LOC for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All Populations Except Adults 50-99 Years)	$BMDL_{10}$ = 3.0 mg/kg	UF_A = 10x UF_H = 10x FQPA SF = 10x	aRfD = 0.03 mg/kg aPAD = 0.003 mg/kg	Acute CCA Study (MRID 46166301) in the rat BMD_{10} = 3.4 mg/kg Inhibition of RBC AChE in female pups (PND 11)
Acute Dietary (Adults 50-99 Years)	$BMDL_{10}$ = 3.0 mg/kg	UF_A = 10x UF_H = 10x FQPA SF = 1x	aRfD = aPAD = 0.03 mg/kg	Acute CCA Study (MRID 46166301) in the rat BMD_{10} = 3.4 mg/kg Inhibition of RBC AChE in female pups (PND 11)
Steady state Dietary (All Populations Except Adults 50-99 Years)	$BMDL_{10}$ = 0.35 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 10x	ssRfD = 0.0035 mg/kg/day ssPAD = 0.00035 mg/kg/day	Repeated-Dose CCA Study (MRID 46166302) in the rat BMD_{10} = 0.52 mg/kg/day Inhibition of RBC AChE in female pups (PND 11)
Steady state Dietary (Adults 50-99 Years)	$BMDL_{10}$ = 0.35 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 1x	ssRfD = ssPAD = 0.0035 mg/kg/day	Repeated-Dose CCA Study (MRID 46166302) in the rat BMD_{10} = 0.52 mg/kg/day Inhibition of RBC AChE in female pups (PND 11)
Incidental Oral (Steady State)	$BMDL_{10}$ = 0.35 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 10x	Residential LOC for MOE < 1000	Repeated-Dose CCA Study (MRID 46166302) in the rat LOAEL = 10 mg/kg/day Inhibition of RBC AChE inhibition in female pups (PND 11)

Table 4.6.4.1 Summary of Toxicological Doses and Endpoints and Points of Departure for Diazinon in Dietary and Non-Occupational Human Health Risk Assessments [a]

Exposure Scenario	Point of Departure (mg/kg/day)	Uncertainty/FQPA Factors	RFD, PAD, & LOC for Risk Assessment	Study and Toxicological Effects
Dermal (Steady State)	NOAEL = 3.0 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 10x	Residential LOC for MOE < 1000	90-Day Dermal Toxicity Study (MRID 48497201) in the rat LOAEL = 10 mg/kg/day Inhibition of RBC and brain AChE in adult female rat
Inhalation (Steady State)	$BMDL_{10}$ = 0.816 mg/m^3/day = 0.22 mg/kg/day [b]	UF_A = 10x UF_H = 10x FQPA SF = 10x	Residential LOC for MOE < 1000	21-Day Inhalation Toxicity Study (MRID 41557402) in the rat BMD_{10} = 0.988 mg/m^3/day Inhibition of RBC AChE in adult female rat
Cancer (Oral, Dermal, Inhalation)	Classification: "Not likely to be carcinogenic to humans" based on the lack of evidence of carcinogenicity in mice and rats and no mutagenicity concern.			

[a] Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. BMDL = lower limit of the bench mark dose. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). SF = Safety Factor. PAD = population adjusted dose (a = acute, ss = steady state or maximal AChE inhibition which occurs around 2-3 weeks for OPs and is a specific exposure assessment conducted for OPs instead of the traditional short, intermediate, or chronic assessments. The SS assessment is protective of longer durations of exposure, including chronic.). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. FQPA SF = FQPA Safety Factor.

[b] Value derived as follows: $BMDL_{10}$ = 0.816 mg/m^3/day = 0.000816 mg/L/day. Applying Haber's Law: 0.000816 mg/L × 6 h rat exposure/8 h human exposure × 5 days/week rat exposure/ 5 days/week human exposure = 0.000816 × 6/8 = 0.0006 mg/L. Inhalation absorption assumed to be 100% = 1. Conversion factor for Sprague-Dawley rats = 44 (default respiratory volume divided by default BW for SD rat = 0.165 L/min × 60 min/h / 0.225 kg = 44). Activity Factor = 1 (physical activity affects ventilation rate; a value of 1 approximates rest). Exposure duration = 8 hours. Mg/kg/day = mg/L/day × inhalation absorption × activity factor × conversion factor × exposure duration = 0.0006 mg/L × 1 × 1 × 44 L/h-kg × 8 h = 0.22 mg/kg each day.

Table 4.6.4.2 Summary of Toxicological Doses and Endpoints for Diazinon for Use in Occupational Human Health Risk Assessments [a]

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Factors	LOC for Risk Assessment	Study and Toxicological Effects
Dermal (Steady state)	NOAEL = 3.0 mg/kg/day	UF_A = 10x UF_H = 10x UF_{DB} [b] = 10x	Occupational LOC for MOE < 1000	90-Day Dermal Toxicity Study (MRID 48497201) in the rat BMD_{10} = 8 mg/kg/day LOAEL = 10 mg/kg/day Inhibition of RBC and brain AChE in adult female rat

Table 4.6.4.2 Summary of Toxicological Doses and Endpoints for Diazinon for Use in Occupational Human Health Risk Assessments [a]				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/ FQPA Factors**	**LOC for Risk Assessment**	**Study and Toxicological Effects**
Inhalation (Steady state)	$BMDL_{10}$ = 0.816 mg/m^3/day = 0.22 mg/kg/day [b]	UF_A = 10x UF_H = 10x UF_{DB} [b] = 10x	Occupational LOC for MOE < 1000	21-Day Inhalation Toxicity Study (MRID 41557402) in the rat BMD_{10} = 0.988 mg/m^3/day Inhibition of RBC AChE inhibition in the adult female rat
Cancer (Oral, Dermal, Inhalation)	Classification: "Not likely to be carcinogenic to humans" based on the lack of evidence of carcinogenicity in mice and rats, and no mutagenicity concern.			

[a] Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. BMDL = lower limit of the bench mark dose. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). LOC = level of concern. MOE = margin of exposure. Steady State= steady state or maximal AChE inhibition which occurs around 2-3 weeks for OPs and is a specific exposure assessment conducted for OPs instead of the traditional short, intermediate, or chronic assessments. The steady state assessment is protective of longer durations including chronic. [b] UF_{DB} for occupational dermal and inhalation exposures = database uncertainty factor for uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4).

[b] Value derived as follows: $BMDL_{10}$ = 0.816 mg/m^3/day = 0.000816 mg/L/day. Applying Haber's Law: 0.000816 mg/L × 6 h rat exposure/8 h human exposure × 5 days/week rat exposure/ 5 days/week human exposure = 0.000816 × 6/8 = 0.0006 mg/L. Inhalation absorption assumed to be 100% = 1. Conversion factor for Sprague-Dawley rats = 44 (default respiratory volume divided by default BW for SD rat = 0.165 L/min × 60 min/h / 0.225 kg = 44). Activity Factor = 1 (physical activity affects ventilation rate; a value of 1 approximates rest). Exposure duration = 8 hours. Mg/kg/day = mg/L/day × inhalation absorption × activity factor × conversion factor × exposure duration = 0.0006 mg/L × 1 × 1 × 44 L/h-kg × 8 h = 0.22 mg/kg each day.

4.7 Endocrine Disruption

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic, and chronic durations and assess carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental, and reproductive effects in different taxonomic groups. As part of its reregistration decision for diazinon, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), diazinon is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal

systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP, where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[6] and includes some pesticides scheduled for registration review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors.

Diazinon is on List 1 for which EPA has received all of the required Tier 1 assay data. The Agency has reviewed all of the assay data received for the appropriate List 1 chemicals, and the conclusions of those reviews are available in the chemical-specific public dockets (see Docket EPA-HQ-OPP-2008-0351 for diazinon). For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website.[7]

5.0 Dietary Exposure and Risk Assessment

5.1 Metabolite/Degradate Residue Profile

5.1.1 Summary of Plant and Animal Metabolism

The qualitative nature of the residue in plants and animals (both from treated feed and from dermal applications) is adequately understood. The primary metabolites in plants and animals are oxypyrimidine and dimethyl oxypyrimidine. Diazoxon and hydroxydiazinon were not identified in the metabolism studies. Diazinon is hydrolyzed to pyrimidinol followed by hydroxylation of the isopropyl or methyl group or both, and subsequent O-conjugation to sugars. The metabolism in rotational crops is the same as for directly-treated primary crops.

5.1.2 Summary of Environmental Degradation

Drinking Water Assessment Memo: K. White, 6/1/2016, D418979.

Diazinon enters the environment via direct spray and spray drift onto soil, foliage, and/or water. The environmental fate properties of diazinon along with monitoring data identifying its presence in surface waters, air, and in precipitation indicate that important transport pathways include runoff and spray drift. Volatilization, atmospheric transport, and subsequent deposition of diazinon to aquatic and terrestrial habitats also occur.

Based on diazinon's aerobic soil metabolism and aerobic and anaerobic aquatic metabolism data, diazinon is not considered persistent in the environment, with half-lives on the order of days to

[6] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.

[7] http://www.epa.gov/endo/

weeks (representative half-life values range from 9 to 57 days). Diazinon also degrades via hydrolysis with time to 50% decline (DT_{50}) values of 2 days at pH 4, 12 days at pH 5, and ranging from 62 to 139 days at pH 7 and 9. The dominant degradation process is expected to depend on environmental conditions. At low pH, hydrolysis may be the primary degradation process, while at higher pH, aerobic metabolism will be more important. Diazinon does undergo atmospheric degradation, the half-life estimated for the average 12-hour day time concentration of hydroxyl radicals in the troposphere at 40°C (104°F) was 1.3 hours.

Diazinon is classified as moderately mobile to slightly mobile and has the potential to reach surface water through runoff and soil erosion. Diazinon has the potential to reach groundwater, especially in high-permeability soils with low organic-carbon content and/or the presence of shallow groundwater. Diazinon is semivolatile and may also be transported in air in both the vapor form and associated with particles. Diazinon is oxidized to diazoxon by hydroxyl radicals and ozone. Based on the drinking water treatment data (Acero *et al.*, 2008; Beduk *et al.*, 2011; Chamberlain *et al.*, 2012; Duirk *et al.*, 2009; Magara *et al.*, 1994; Ohashi *et al.*, 1994; Wu *et al.*, 2009; Zhang and Pehkonen, 1999), it is possible that diazoxon could form in air in the presence of ozone.

The only identified degradate of concern for diazinon is diazoxon. Diazoxon has been identified as a residue of concern for both human health and ecological risk assessments. Diazoxon was only observed in one submitted aerobic soil metabolism study at a maximum of 0.6% applied radioactivity and in an air photolysis study where it formed before the photolysis portion of the study began. Limits of quantitation for diazoxon were high (0.01 to 0.02 mg/kg-soil) in the studies where it was examined, and there was a portion of unidentified residues in submitted laboratory studies. Although formation and degradation of diazoxon cannot be quantified from available laboratory fate studies involving diazinon, diazoxon has been detected in air, rain, fog (Majewski and Capel, 1995) and surface waters in the United States (USGS, 2011). Organophosphates that contain a phosphothionate group (P=S), such as diazinon, are known to transform to the corresponding oxon analogue containing a phosphorus-oxygen double bond (P=O) instead. This transformation occurs via oxidative desulfonation and can occur through photolysis and aerobic metabolism, as well as other oxidative processes. Disinfection with chlorine or ozone converts diazinon to diazoxon (Acero *et al.*, 2008; Beduk *et al.*, 2011; Chamberlain *et al.*, 2012; Duirk *et al.*, 2009; Magara *et al.*, 1994; Ohashi *et al.*, 1994; Wu *et al.*, 2009; Zhang and Pehkonen, 1999) and similar reactions with ozone could occur in the natural environment. In surface water monitoring data wherein residues of both diazinon and diazoxon were detected, the ratios of the concentrations of diazoxon to diazinon ranged from 0 to 0.5.

5.1.3 Comparison of Metabolite Pathways

The metabolic pathway of diazinon in plants, animals, and water appears very similar, and results in primarily oxy pyrimidines and/or their glucose conjugates. Hydroxydiazinon and diazoxon are not found in plant and animal metabolism studies, but diazoxon may be found in water; data on drinking water treatment suggests that in many water treatment facilities diazinon will degrade rapidly to diazoxon. In the rat metabolism study, three major metabolites were identified in the urine to indicate that diazinon is metabolized to liberate the pyrimidinyl group that is oxidized and excreted. Only trace amounts of parent diazinon were present in the urine or feces.

5.1.4 Residues of Concern Summary and Rationale

The HED Metabolism Committee has determined the residues of concern in plants and animals (*Diazinon: Decision from the HED Metabolism Assessment Review Committee*, D. Hrdy, 4/17/98, D244848). The committee recommended that for enforcement purposes parent compound diazinon be included in the tolerance expression and that residues of diazinon and its metabolites, hydroxydiazinon and diazinon oxon (diazoxon), be considered in dietary risk assessment. Implicit in the committee decision was the provision that metabolites would be included only if they were found to be present or if their level could be reliably estimated in foods. Although hydroxydiazinon and diazoxon were not identified in the available plant and animal metabolism studies, the metabolites were not excluded as potential residues of concern, because they are cholinesterase inhibitors.

The residues of concern in drinking water are diazinon and diazoxon. 100% conversion of diazinon to the oxon in water is assumed for the dietary risk assessment.

Table 5.1.4. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression.

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Diazinon, hydroxydiazinon, diazoxon[1]	Diazinon
	Rotational Crop	Diazinon, hydroxydiazinon, diazoxon	Diazinon
Livestock	Ruminant	Diazinon, hydroxydiazinon, diazoxon	Diazinon
	Poultry	Diazinon, hydroxydiazinon, diazoxon	Diazinon
Drinking Water		Diazinon, diazoxon	Not Applicable

[1] diazinon oxon

5.2 Residue Chemistry and Food Residue Profile

Residue Chemistry Memo: D. Drew, 12/1/2000, D270422.
Residue Chemistry Memo: D. Drew, 4/22/2014, D419217.
Dietary Assessment Memo: D. Drew, 5/3/2016, D426970.

Residue Chemistry

Tolerances are established for residues of diazinon in a wide variety of crops and in cattle fat (40 CFR §180.153). This section provides the status of residue chemistry requirements for diazinon and includes residue data submitted and reviewed since the Registration Eligibility Decision (RED) for diazinon [7/31/06; Interim RED (IRED) issued 5/2004].

The following residue chemistry data requirements were identified in the 2004 diazinon IRED: Guideline 860.1500, additional magnitude of the residue data for blueberries, celery, spinach, and Swiss chard. Residue studies for the above crops have been received and reviewed by the

HED [D419217, 4/22/14; MRIDs 46829401 (blueberry), 45371214 (celery), 46829402 (spinach), 45371204 (spinach), 45371205 (spinach), and 45371208 (Swiss chard)]. HED has concluded that the residue data deficiencies cited in the 2004 IRED for the above crops (blueberries, celery, spinach, and Swiss chard) have been fulfilled. The summary and the regulatory implication of the study results (by crop) are presented in Appendix F.

Food Residue Profile

HED has previously evaluated residue data depicting the magnitude of diazinon residues of concern in/on all registered crops. Quantifiable residues of diazinon were found in crops with short pre-harvest intervals (PHIs), resulting in tolerance levels of up to 3.0 ppm in food commodities. The only tolerance for livestock commodities is for cattle fat at 0.5 ppm (based on cattle ear tag studies). There is "no reasonable expectation of finite residues" (Category 40CFR 180.6(a)(3) for all other livestock commodities.

Extensive PDP food monitoring data for residues of diazinon in a wide variety of commodities are available. The majority of foods monitored had no detectable residues of diazinon. Of the food commodities that had detectable residues, only four had samples with detects that were greater than 1% of the number of samples tested. Those commodities were apples (7.4% detects), carrots (5.3% detects), collards (3.1% detects) and kale (3.4% detects).

The dietary residues of concern in food are diazinon and its metabolites diazoxon and hydroxydiazinon. Because these metabolites are never or seldom (and only near the limit of detection) found in monitoring data or empirical studies, residues of hydroxydiazinon and diazoxon are assumed to be zero in the dietary food assessment.

5.3 Water Residue Profile

Drinking Water Assessment Memo: K. White, 6/1/2016, D418979.

The Environmental Fate and Effect Division (EFED) provided EDWCs for use in the human health risk assessment in *Diazinon Registration Review Drinking Water Assessment* (White, K., 6/1/2016, D418979). The following drinking water data summary is excerpted from that memorandum.

Residues of concern for human health in drinking water have been identified as diazinon and diazoxon. Models were not used to simulate EDWCs for diazoxon because not enough data are available for a full model simulation. Data on drinking water treatment suggest that in many water treatment facilities diazinon will degrade rapidly to its more toxic degradate diazoxon, where diazoxon may be stable. In other treatment facilities, diazinon may be degraded to other degradates or will have a low level of removal. To provide an estimate of potential diazoxon concentrations in drinking water, diazinon concentrations were converted to diazoxon concentrations using a molecular weight conversion factor (0.947) and assuming that 100% of diazinon was converted to diazoxon. The EDWCs for both surface water and groundwater recommended for use in HED's human health dietary risk assessment are summarized in D418979.

For surface water sources of drinking water, the Pesticides in Flooded Agriculture Model (PFAM) modeled maximum (1-in-10 year return frequency) acute EDWCs associated with diazinon use on cranberries was 141 µg/L. This EDWC may overestimate actual concentrations

in drinking water. The estimated concentration represents residues in the bog, post-flood. This concentration is not expected to correspond with concentrations occurring outside of cranberry bogs where drinking water intakes are located. While these model results are generally expected to overestimate human exposure, monitoring data suggest that residues of diazinon may occur within an order of magnitude lower of the modeled PFAM peak EDWC. The annual average EDWC from PFAM is higher than what is expected to occur and was, therefore, not recommended for use in the drinking water assessment. Cranberry use was also modeled using SWCC.

The next highest 21-day average EDWC was generated by the simulation of use on apples and/or pears. It reflects two foliar applications of diazinon (to apple or pear tree orchards) at 2 lbs active ingredient per acre (lbs a.i./A) with a 14-day retreatment interval. The associated 1-in-10 year peak and annual average EDWCs were 110 and 8.85 µg/L, respectively. A simulation of the use of diazinon on melons at 4 lbs a.i./A with soil incorporation, followed by a foliar application at 0.75 lbs a.i./A, resulted in a peak and annual average EDWC of 119 and 7.09 µg/L, respectively. These simulations of EDWCs using the Surface Water Concentration Calculator (SWCC) reflect potential surface water concentrations in runoff-vulnerable locations where apples, pears, or melons are grown and diazinon is applied over a large portion of the watershed. It is not expected that these high EDWCs represent concentrations in all waters in apple, pear, or melon growing areas nationally. It is estimated by the Biological and Economic Analysis Division (BEAD) that approximately 30,000 lbs of diazinon per year was applied to apples and pears between 2004 and 2012, indicating that this is an important use pattern for diazinon. These peak EDWCs are similar to diazinon concentrations measured in a pond adjacent to an application area in an aquatic field dissipation study (peak=113 µg/L), and are higher, although within an order of magnitude, than maximum concentrations detected in ambient surface water monitoring for parent diazinon.

Based on the EFED recommendations, HED has selected the bolded values in Table 5.3 as appropriate for inclusion in the steady state and acute diazinon dietary risk assessments as these values represent a bounding range of low- and high-end EDWCs based on the maximum allowed application rate scenarios. The SWCC values for cranberry (20.5 ug/L for acute and 15.3 ug/L for steady state) were used directly in the dietary model as point estimates. For the apple/pear (PA apple) and melon (FL cucumber) drinking water scenarios, a distribution of surface water residues was used probabilistically in the dietary model. The following paragraph describes the derivation of those distributions.

Daily time-series outputs that simulate 29 years (1962-1990) of residues of diazinon in surface drinking water from the apple/pear (PA apple) and melon (FL cucumber) scenarios were modeled using the SWCC. All of the time-series data were adjusted to reflect 100% conversion of diazinon to diazoxon by adjustment for molecular weight and by multiplying the residues by the acute (12x) and steady state (9x) TAFs. No further adjustments were made to the acute distribution files, but since the steady state average dietary assessments use 21-day forward rolling averages for drinking water, the steady state distributions were further adjusted to be 21-day forward rolling averages. In the 21-day rolling average distributions, the first data point is the average of days 1-21, the second data point is the average of days 2-22, the third data point is the average of days 3-23, etc. The 21-day rolling average continues until the last 20 days of residues of the final distribution year.

Table 5.3 EDWCs for Residues of Diazinon and Diazoxon[a]					
Drinking Water Source (Model)	Use and Rate Modeled	Diazinon Concentration in Drinking Water (µg/L)[b] (Diazoxon concentration)[a]			
		1-in-10 Year Peak	1-in-10-year 21-day Ave	1-in-10 Year Annual Ave (SWCC) or Post Breakthrough Ave (PRZM-GW)	30 Year Mean
Surface Water[e] (PFAM)	Cranberries 3 lbs a.i./A, 3x, 14d MRI, foliar ground	141[c] (134)	131[c] (124)	--	--
Surface Water[e] (SWCC)	Cranberries 3 lbs a.i./A, 3x, 14d MRI, foliar ground	21.7[d] (20.5)	16.2[d] (15.3)	3.82[d] (3.62)	3.82[d] (2.54)
Surface water (SWCC)	Apples or Pears 2 lbs a.i./A, 2x, 14d MRI, foliar ground	110 (104)	65.8 (62.3)	8.85 (8.38)	4.25 (4.02)
Surface Water (SWCC)	Melons 4 lbs a.i./A, 1x with 2 inch soil incorporation, 0.75 lbs a.i./A 1x, foliar ground	119 (113)	62.9 (59.6)	7.09 (6.71)	3.56 (3.37)
Groundwater (PRZM-GW)	CA Nursery 5 lbs a.i./A, 12x, 14d MRI, foliar, ground	2.37 (2.24)	--	1.72 (1.63)	--

MRI=minimum retreatment interval; Ave=Average

[a] The molecular weight conversion to diazoxon is 0.947. EDWCs for diazoxon would be approximately 0.947 of the reported diazinon concentration if chlorination and/or other processes converted all diazinon to diazoxon.

[b] Drinking water concentrations were modeled for residues of diazinon plus lost radioactivity and residues of diazinon alone based on some uncertainty about aerobic soil metabolism study results with substantial lost radioactivity. Most lines of evidence suggest that diazinon is not persistent; therefore, the EDWCs reflecting residues of diazinon alone are recommended for use in the exposure assessment and shown in this table for surface water. However, it should be noted that there is some uncertainty as to whether there may be some vulnerable areas where the aerobic soil metabolism DT_{50} would be higher than the DT_{50} of 34-days used to determine these EDWC. There is one measured DT_{50} for aerobic soil metabolism of 56 days. The PRZM-GW results reflect residues of diazinon and lost radioactivity and the aerobic soil metabolism input value was 155-days.

[c] Calculated using PFAM, reflects concentrations in water that could be released from the cranberry bog.

[d] Calculated using the SWCC.

[e] The primary area of concern for cranberries and drinking water is in Massachusetts as this is an area with a high mass of diazinon applied per year and drinking water intakes located near cranberry growing areas.

Water Monitoring Data

There are several monitoring studies, and data from several sources, available on diazinon residues in drinking water (raw and finished), surface water, groundwater, sediment, tissue (fish and mussels), air, rain, and snow. Most studies were not specifically targeted at diazinon, or were collected in agricultural areas during the season of pesticide use, but the frequency of

sample collection was not adequate to ensure the capture of peak concentrations. The data are useful in that they provide some information on the occurrence of diazinon in the environment under existing usage conditions. However, the measured concentrations should not be interpreted as reflecting the upper end of potential exposures. Targeted monitoring, wherein application dates and amounts of applied materials are known, and concentrations are followed in relation to the application(s) are discussed in the summarized field dissipation data. Changes in diazinon use patterns were implemented between 2004 and 2008, after the Reregistration Eligibility Decision was completed. Updates included cancellation of non-agricultural uses (except nurseries), seed treatment uses, cancellation of granular formulations, and only allowing aerial applications of diazinon to lettuce. Thus, monitoring conducted prior to this period may not reflect current use patterns of diazinon. In order to evaluate whether changes in the observed monitoring results reflect changes in use patterns, the frequency and location of monitoring and how it relates to usage information in the area monitored must be considered.

Diazinon is one of the most frequently detected pesticides in surface water and has been detected in 46 states, in every major river basin (including the Mississippi, Columbia, Rio Grande, and Colorado), and in large rivers and major aquifers. The highest known diazinon concentration detected in surface water was 61.9 µg/L in a creek in California in 2009. Eleven states had surface water detections at 0.9 µg/L or greater and 34 states had detections above 0.1 µg/L. Detections greater than 1 µg/L are still occurring after 2007, when several mitigations on diazinon use[8] were implemented, with concentrations above 0.1 µg/L being common, especially in high use areas. Additionally, analysis of the locations of drinking water intakes in relation to the locations where surface water monitoring occurred, shows that detections have occurred in and near waters with drinking water intakes. Diazinon has been detected in raw drinking water samples. Diazoxon was also detected in surface water at a maximum concentration of 0.43 µg/L.

Diazinon has also been detected in groundwater, sediment, air, precipitation, and tissue (fish, clam, and mussel) but at lower concentrations and/or detection frequencies. The highest concentration reported in fish fillet was 140 ng/g wet-weight. The highest diazinon concentration detected in groundwater was 19 µg/L; however, the detection frequency in groundwater is much lower than that in surface water. Much of the monitoring data available are non-targeted (not specific to a particular diazinon application), and sampling did not occur with sufficient frequency to capture peak concentrations, except perhaps by accident. Therefore, monitoring data should not be assumed to define the upper bound of potential real world exposures. While it may be helpful to compare monitoring results with modeled values, the two are not expected to be similar. Modeled EDWCs represent concentrations in a runoff-vulnerable reservoir, while monitoring reflects a range of waterbodies and use areas. Monitoring results provide one line of evidence about whether concentrations in the environment are at or near levels where risk may occur.

5.4 Dietary Risk Assessment

Dietary Assessment Memo: D. Drew, 5/3/2016, D426970.

5.4.1 Description of Residue Data Used in Dietary Assessment

[8] RED mitigations include cancellation of residential uses, seed treatments, and use of granules. Additionally, most aerial applications were cancelled. While these mitigations were implemented in prior to 2008, it may have taken some time for all products to be removed from the market.

Refined acute and steady state dietary (food and drinking water) exposure and risk assessments for diazinon were conducted using DEEM-FCID version 3.18. This model uses 2003-2008 food consumption data from USDA's National Health and Nutrition Examination Survey, What We Eat in America (NHANES/WWEIA). All food commodities with associated tolerances for residues of diazinon were included in the dietary assessments except for grape and mushroom commodities. There are no registered uses of diazinon on grape and mushroom, and the tolerance expiration date for those crops is listed in the 40 CFR 180.153 as 9/10/2010.

Extensive PDP monitoring data for residues of diazinon in a wide variety of commodities are available. Both the acute and steady state assessments were refined using distributions and point estimates derived from PDP monitoring data, PCT data, and default or empirical processing factors. If monitoring data were not available for a particular commodity but were available for a similar commodity, the available data were translated to the similar crop. HED SOP 99.3, HED SOP 2000.1, and use pattern information were used as guidance for translations. When data were translated, the residue-distribution file (RDF) was adjusted to account for differences in PCT. All food residues in the diazinon assessments were derived from PDP monitoring, except for figs. Residue values for figs were derived from fig field trial data, since appropriate monitoring data were not available for this commodity. Default DEEM processing factors, where available, were applied to processed foods, except for tomato juice and pineapple juice. Processing factors for tomato juice and pineapple juice were derived from empirical data.

The HED metabolism committee recommended that residues of diazinon and its metabolites, hydroxydiazinon and the diazinon oxon (diazoxon), be considered in dietary risk assessment. Implicit in the committee decision was the provision that metabolites would be included only if they were found to be present or if their level could be reliably estimated in foods. The PDP monitoring program analyzed for the diazoxon in > 90,000 samples from numerous crops. From 1999 to 2008, residues of the oxon metabolite were <LOD in/all samples except for five samples where the oxon residues were near the method levels of detection. No oxon residues were detected in any of the more recent PDP samples (between 2009 and 2013). Neither hydroxydiazinon nor diazoxon were found in five different diazinon metabolism studies (apples, lettuce, corn, potatoes, and green beans) or in animal metabolism studies (both oral and dermal studies). Typically, for OPs with a metabolites of toxicological concern, the residues in food are adjusted to include the metabolites and any toxicity adjustment factors (TAFs). Given the preponderance of evidence indicating that diazoxon and hydroxydiazinon are not expected in food, including these metabolite residues in foods (even at a half LOD anticipated residue) would lead to a large overestimate of actual exposure; therefore, residues of hydroxydiazinon and diazoxon in food are assumed to be zero in the dietary assessment.

5.4.2 Percent Crop Treated Used in Dietary Assessment

BEAD provided a March 25, 2015 Screening Level Usage Analysis (SLUA) for diazinon. The acute and steady state analyses incorporated the following maximum PCT data reported in the SLUA: Almonds 10%, Apples 10%, Apricots 40%, Beans, Green 5%, Blueberries 25%, Broccoli 20%, Brussels Sprouts 45%, Cabbage 25%, Caneberries 50%, Cantaloupes 35%, Carrots 40%, Cauliflower 20%, Celery 10%, Cherries 15%, Cucumbers 10%, Figs 20%, Lettuce 60%, Nectarines <2.5%, Onions 25%, Peaches 15%, Pears 10%, Peas, Green <2.5%, Pecans <2.5%, Peppers 10%, Plums/Prunes 25%, Potatoes <2.5%, Spinach 60%, Squash 10%, Strawberries 15%, Tomatoes 10%. For crops where no PCT data were provided, a conservative 100% crop treated was assumed.

5.4.3 Acute Dietary Risk Assessment

The acute (food only) exposure estimates are not of concern (did not exceed 100% of the acute population adjusted dose (aPAD)) for the U.S. population and all population subgroups at the 99.9th percentile. Food exposures for the U.S. population utilized 6.0% of the aPAD. Food exposures for children 1-2 years old, the most highly exposed population subgroup, utilized 15% of the aPAD.

The acute exposure estimates for drinking water only for the most highly-exposed population subgroups (infants and children ages 1-2) exceed 100% of the aPAD at the 95th percentile of exposure (> 140% of the aPAD).

A stepwise approach is used to calculate aggregate dietary (food and water) exposure and risk to diazinon and diazoxon. If a risk of concern is identified for any population subgroup in any of the steps, the exposure and risk estimates for the "next step" of the assessment are not calculated, since they would also result in risks of concern. Since dietary exposures from drinking water alone were of concern for the highest exposed subpopulations (infants and children), drinking water exposures were not combined with exposures from food for these or any other population subgroups. Combining those exposures would result in even greater risk estimates of concern. The acute aggregate dietary (food and water) exposures and risk estimates are of concern.

The acute dietary assessment results are in tables 5.4.6.1 and 5.4.6.3 below.

5.4.4 Steady State Dietary Risk Assessment

The steady state dietary (food only) exposure estimates are not of concern (did not exceed 100% of the steady state population adjusted dose (ssPAD)) for the U.S. population and all population subgroups at the 99.9th percentile. Food exposures for the U.S. population utilized 41% of the ssPAD. Food exposures for children 1-2 years old, the most highly exposed population subgroup, utilized 100% of the ssPAD.

The steady state exposure estimates for drinking water only for the most highly-exposed population subgroups (infants and children ages 1-2) exceed 100% of the ssPAD at the 95th percentile of exposure (> 1400% of the ssPAD).

Since dietary exposures from drinking water alone were of concern for the highest exposed subpopulations (infants and children), drinking water exposures were not combined with exposures from food. Combining those exposures would result in even greater risk estimates of concern. The steady state aggregate dietary (food and water) exposures and risk estimates are of concern.

The steady state dietary assessment results are in tables 5.4.6.2 and 5.4.6.4 below.

5.4.5 Cancer Dietary Risk Assessment

Diazinon is classified as a "not likely to be carcinogenic to humans." Therefore, a quantitative cancer dietary assessment is not required.

5.4.6. Dietary Assessment Summary Tables

Table 5.4.6.1. Summary of Acute Dietary (Food Only) Exposure and Risk for Diazinon.

Population Subgroup	aPAD (mg/kg/day)[1]	95th Percentile		99th Percentile		99.9th Percentile	
		Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD
General U.S. Population	0.003	0.000020	<1	0.000052	1,7	0.000179	6.0
All Infants (<1 year old)		0.000066	2.2	0.000130	4.3	0.000290	9.7
Children 1-2 years old		0.000071	2.4	0.000159	5.3	0.000457	15
Children 3-5 years old		0.000047	1.6	0.000092	3.1	0.000359	12
Children 6-12 years old		0.000027	<1	0.000053	1.8	0.000226	7.5
Youth 13-19 years old		0.000014	<1	0.000027	<1	0.000125	4.2
Adults 20-49 years old		0.000014	<1	0.000029	<1	0.000134	4.5
Adults 50-99 years old		0.000016	<1	0.000032	<1	0.000014	<1
Females 13-49 years old		0.000014	<1	0.000029	<1	0.000142	4.7

[1]Includes 10X FQPA SF for all population subgroups except adults 50-99 years old. The aPAD for adults 50-99 years old is 0.03 mg/kg/day

Table 5.4.6.2. Summary of Steady State Dietary (Food Only) Exposure and Risk for Diazinon.

Population Subgroup	ssPAD[1] (mg/kg/day)	95th Percentile		99th Percentile		99.9th Percentile	
		Exposure (mg/kg/day)	% ssPAD	Exposure (mg/kg/day)	% ssPAD	Exposure (mg/kg/day)	% ssPAD
General U.S. Population	0.00035	0.000018	5.1	0.000046	13	0.000142	41
All Infants (<1 year old)		0.000053	15	0.000125	36	0.000282	81
Children 1-2 years old		0.000063	18	0.000125	36	0.000352	100
Children 3-5 years old		0.000043	12	0.000081	23	0.000269	77
Children 6-12 years old		0.000021	6.1	0.000048	14	0.000175	50
Youth 13-19 years old		0.000011	3.3	0.000023	6.5	0.000097	28
Adults 20-49 years old		0.000012	3.6	0.000025	7.2	0.000101	29
Adults 50-99 years old		0.000014	<1	0.000030	<1	0.000099	2.8
Females 13-49 years old		0.000012	3.5	0.000026	7.3	0.000105	30

[1]Includes 10x FQPA SF for all population subgroups except adults 50-99 years old. The ssPAD for adults 50-99 years old is 0.0035 mg/kg/day.

Table 5.4.6.3. Summary of Diazinon ACUTE Assessment Results for Maximum Application Rate Drinking Water Scenarios (Water Only: 95th Percentile).				
Drinking Water Use Site (Scenario)	Acute WATER ONLY (All Infants <1 year old)		Acute WATER ONLY (Children 1-2 years old)	
	95th		95th	
	Exposure (mkd)	% aPAD	Exposure (mkd)	% aPAD
Cranberry (OR berries)[1]	0.042697	1400	0.021021	700
Melon (FL cucumber)[2]	0.010808	360	0.006058	200
Apple/Pear (PA apple)[2]	0.007869	260	0.004141	140

mkd= mg/kg/day.
[1] Point estimate EDWC used.
[2] Distribution of EDWCs used.

Table 5.4.6.4. Summary of Diazinon STEADY STATE Assessment Results for Maximum Application Rate Drinking Water Scenarios (Water Only: 95th Percentile).				
Drinking Water Use Site (Scenario)	Acute WATER ONLY (All Infants <1 year old)		Acute WATER ONLY (Children 1-2 years old)	
	95th		95th	
	Exposure (mkd)	% ssPAD	Exposure (mkd)	% ssPAD
Cranberry (OR berries)[1]	0.029375	8400	0.013793	3900
Melon (FL cucumber)[2]	0.008929	2600	0.004884	1400
Apple/Pear (PA apple)[2]	0.154796	>10000	0.040168	>10000

mkd= mg/kg/day.
[1] Point estimate EDWC used.
[2] Distribution of EDWCs used.

6.0 Residential and Other Non-Occupational Exposure and Risk Estimates

ORE memo: S. Tadayon, 6/10/2016, D426969.

All indoor and pet uses of diazinon were voluntarily cancelled effective November 15, 2001 (66 FR 5744) and all outdoor non-agricultural uses were voluntarily cancelled effective August 11, 2004 (69 FR 48864). All the available products are classified as Restricted Use Products (RUP) and may be purchased and used only by certified applicators or persons under their direct supervision.

7.0 Non-Occupational Spray Drift Exposure and Risk Estimates

Off-target movement of pesticides can occur via many types of pathways, and this movement is governed by a variety of factors. Sprays that are released and do not deposit in the application area end up off-target and can lead to exposures to those people it may directly contact. Spray can also deposit on surfaces where contact with residues can eventually lead to indirect exposures (*e.g.*, children playing on lawns where residues have deposited next to treated fields). The potential risk estimates from these residues can be calculated using drift modeling onto 50 feet wide lawns coupled with methods employed for residential risk assessments for turf products.

The approach to be used for quantitatively incorporating spray drift into risk assessment is based on a premise of compliant applications which, by definition, should not result in direct exposures to individuals because of existing label language and other regulatory requirements intended to prevent them.[9] Direct exposures would include inhalation of the spray plume or being sprayed directly. Rather, the exposures addressed here are thought to occur indirectly through contact with impacted areas, such as residential lawns, when compliant applications are conducted. Given this premise, exposures for children (1 to 2 years old) and adults who have contact with turf where residues are assumed to have deposited via spray drift (thus resulting in an indirect exposure) are the focus of this analysis, analogous to how exposures to turf products are considered in risk assessment.

In order to evaluate the drift potential and associated risks, an approach based on drift modeling coupled with techniques used to evaluate residential uses of pesticides was utilized. Essentially, a residential turf assessment based on exposure to deposited residues has been completed to address drift from the agricultural applications of diazinon. In the spray drift scenario, the deposited residue value was determined based on the amount of spray drift that may occur at varying distances from the edge of the treated field using the AgDrift (v2.1.1) model. Exposures were considered for 50 feet wide lawns where the nearest side of the property was directly adjoining the treated field (at field edge) and at varied distances up to 300 feet downwind of a treated field. Once the deposited residue values were determined, the remainder of the spray

[9] This approach is consistent with the requirements of the EPA's Worker Protection Standard.

drift assessment was based on the algorithms and input values specified in the recently revised (2012) *Standard Operating Procedures for Residential Risk Assessment (SOPs)*.

A screening approach was developed for situations where specific label guidance for application parameters was not available.[10] AgDrift is appropriate for use only when applications are made by aircraft, airblast sprayers, and groundboom sprayers. When AgDrift was developed, a series of screening values (i.e., the Tier 1 option) were incorporated into the model and represent each equipment type and use under varied conditions. The screening options specifically recommended in this methodology were selected, because they are plausible and represent a reasonable upper bound level of drift for common application methods in agriculture. In all cases, each scenario is to be evaluated, unless it is not plausible based on the anticipated use pattern (e.g., herbicides are not typically applied to tree canopies) or specific label prohibitions (e.g., aerial applications are not allowed). Section 7.1 provides the screening level drift related risk estimates along with additional risk management options if necessary. These drift estimates represent plausible options for pesticide labels.

Dermal or incidental oral exposure to diazoxon from contact with turf where residues are assumed to have deposited via spray drift are not anticipated. No occupational exposure studies (DFR) were identified that quantified the levels of oxon present in the environment. Further, as noted above in Section 5.4.1, the dietary exposure risk assessment concludes that "all residues in food are assumed to be parent diazinon, since diazoxon is not typically found in foods, in monitoring data, or crop field trials" indicating that the oxon would also not be expected to occur on turf from agricultural spray drift.

7.1 Combined Risk Estimates from Lawn Deposition Adjacent to Applications

The spray drift risk estimates are based on an estimated deposited residue concentration as a result of the screening level agricultural application scenarios. Diazinon is used on a variety of crops and can be applied via airblast, groundboom and aerial equipment at a maximum application rate of 4 lbs ai/acre. The recommended drift scenario screening level options are listed below:

- **Groundboom applications** are based on the AgDrift option for high boom height and using very fine to fine spray type using the 90th percentile results.

- **Aerial applications** are based on the use of AgDrift Tier 1 aerial option for a fine to medium spray type and a series of other parameters which will be described in more detail below (e.g., wind vector assumed to be 10 mph in a downwind direction for entire application/drift event).

- **Orchard airblast applications** are based on the AgDrift option for Sparse (Young/Dormant) tree canopies.

[10] http://www.agdrift.com/

In addition to the screening level spray drift scenarios described above, additional results are provided which represent viable drift reduction technologies (DRTs) that represent potential risk management options. In particular, different spray qualities have been considered as well as the impact of other application conditions (e.g., boom height, use of a helicopter instead of fixed wing aircraft, crop canopy conditions).

Dermal risk estimates were calculated for adults. Dermal and incidental oral risk estimates for children 1<2 years old were combined, because the toxicity endpoint for each route of exposure is the inhibition of RBC cholinesterase (ChE). The total applicable Level of Concern is 1000 so MOEs < 1000 represent risk estimates of concern.

Adult dermal and children's (1 to < 2 year old) dermal and incidental oral risk estimates related to spray drift are of concern at the field edge, and result in a range of buffers depending on the spray drift scenario. These are summarized in Table 7.1.1 (All drift calculations are provided in the most recent ORE memo (S. Tadayon, 6/10/2016, D426969). Results indicate that the major risk concern is from aerial applications. Appropriate drift reduction technologies such as changing the spray type/nozzle configuration to coarser spray applications may result in less drift and reduced risk concerns (i.e., higher MOEs) from aerial applications. Similarly, using coarser sprays and lowering boom height for groundboom sprayers reduces risk concerns. A summary of spray drift buffers is presented in Table 7.1.1.

Table 7.1.1. Summary of Spray Drift Buffers for Diazinon.

Crop Category	Crops	Application rate (lb ai/A)	Adult Buffer Summary			Children 1 < 2 years Buffer Summary (Dermal + Incidental Oral)		
			Buffers (feet) Necessary to reach MOE of 1000			Buffers (feet) Necessary to reach MOE of 1000		
			Aerial	Groundboom	Airblast	Aerial	Groundboom	Airblast
Typical Acreage Crops	Beans(All Types), Beets, Broccoli, Brussels Sprouts, Cabbage, Cane berries, Carrot, Cauliflower, Collard, Cranberry, Cucumber, Endive, Fig, Kale, Melons (all types), Mustard, Onion (all types), Peas, Pepper, potato, Prune, Radish, Rutabaga, Shallot, Spinach, Tomato, Turnip	4	NA	>300	NA	NA	>300	NA
	Blackberry, Dewberry, Lettuce, Loganberry and Rasberry	2		125->300			200	
	Lettuce	2	>300	125->300		>300	>300	
	Pineapple, Strawberry	1		50 - 150			125-300	
	Blueberry, Water cress, Ginseng	0.5		10 - 50			50-.>300	
Orchard	Apple, Apricot, Blueberry, Boysenberry, Cane berry, Cherry, Fig, Filbert, Nectarine, Peach, Pear, Plum, Prune	2.0	NA	NA	0-150	NA		25-250
	Filbert	0.5			0-75			

Table 7.1.1. Summary of Spray Drift Buffers for Diazinon.								
Crop Category	**Crops**	**Application rate (lb ai/A)**	**Adult Buffer Summary**			**Children 1 < 2 years Buffer Summary (Dermal + Incidental Oral)**		
			Buffers (feet) Necessary to reach MOE of 1000			**Buffers (feet) Necessary to reach MOE of 1000**		
			Aerial	**Groundboom**	**Airblast**	**Aerial**	**Groundboom**	**Airblast**
								0-100
	Almond	3.0			10-200			50-250

8.0 Residential Bystander Post-Application Inhalation Exposure

The Agency has also developed a preliminary bystander volatilization inhalation exposure assessment for diazinon utilizing the currently available inhalation toxicity and air monitoring data. There are six air monitoring studies available for diazinon that were conducted at the request of California Department of Pesticide Regulation (CDPR)[11]. The list of studies is presented below:

- Air Monitoring of an Orchard Application of Diazinon in Glenn County during January of 2010.
- Ambient Air Monitoring For Diazinon and Diazoxon in Monterey, San Benito and Santa Clara Counties during July and August of 2009.
- Ambient Air Monitoring for Pesticides in Lompoc, California.
- The Application (Kings County) and Ambient (Fresno County) Air Monitoring of Diazinon during winter, 1998.
- Ambient Air Monitoring of Diazinon in Fresno County during winter 1997.
- Aerial Movement and Deposition of Diazinon, Chlorpyrifos, and Ethyl Parathion.

HED conducted a conservative volatilization assessment, using the air monitoring data in Glen County, California conducted during January 2010, which resulted in the highest air concentrations of the studies noted above. In this study, the Air Resources Board (ARB) conducted application air monitoring for the insecticide, diazinon, and the oxygen analog, diazoxon, in Glenn County from January 4 through 7, 2010. A total of 41 air samples, along with 10 quality control (QC) samples, were collected at eight sites around a 19 acre plum (prunes) orchard in northeastern Glenn County, CA.

The reported diazinon air concentrations ranged from less than the method detection limit (MDL; 6 ng/sample) to 4,261 ng/m^3. Thirty-five of the 41 samples were greater than the MDL and 31 were greater than the estimated quantitative level (EQL; 30 ng/sample). The reported diazoxon air concentrations ranged from less than the MDL (20 ng/sample) to 124 ng/m^3. Twenty-four of the 41 samples exceeded the MDL and seven (7) exceeded the EQL of 100 ng/sample (the summary of air monitoring results is presented in Table 7.1 of D426969).

[11] http://www.cdpr.ca.gov/docs/emon/pubs/tac/diazinon.htm

Table 8.1 below provides the diazinon inhalation risk estimates from volatilization. The comparison of the mean air concentration values against the steady state POD ($BMDL_{10}$ = 0.816 mg/m^3) is a reasonable match of the toxicological effect and exposure profile. This arithmetic mean comparison was completed to represent the potential for a seasonal exposure profile. The peak air concentration was also compared to the steady state POD (there are no available acute inhalation data from which to derive an acute inhalation POD), and this is considered a conservative assessment of potential risk. There are risk estimates of concern (i.e., MOEs <1000) for bystander volatilization inhalation for both single day and steady state exposure scenarios.

Table 8.1 Residential Bystander: Preliminary Volatilization Risk Analysis for Diazinon Air Monitoring Data.

Study	Sampler/ Site Location	Number of samples	Duration of samples	Duration of sampling period	Maximum Air Conc (mg/m^3)	Arithmetic Mean Air Conc (mg/m^3)*	Single-Day MOEs[a] (LOC = 1000)	Steady state MOEs[b] (LOC = 1000)
Air Monitoring of an Orchard Application of Diazinon in Glenn County during January of 2010	8 sites located around field	40 (1 less than the MDL for diazinon and 13 for diazoxon)	5.3 to 16.5 hours	January 04– January 07, 2010	4.31E-03	1.06E-03	190	770

Single Day MOE = Steady state HEC (0.816 mg/m^3) / Study maximum air concentration (mg/m^3). LOC = 1000.
Steady state MOE = Steady state HEC (0.816 mg/m^3) / Study arithmetic mean air concentration (mg/m^3). LOC = 1000.
* Diazinon + diazoxon concentrations
Conc = concentration

9.0 Aggregate Risk Assessments

9.1 Acute Aggregate Risk

The acute exposure estimates provided in the Dietary Exposure Section 5.4 represent the acute aggregate exposure. The acute aggregate dietary (food and water) exposures and risk estimates for the registered uses of diazinon are of concern. The acute (food only) exposure estimates are not of concern (did not exceed 100% of the aPAD) for the U.S. population and all population subgroups. Food exposures for children 1-2 years old, the most highly exposed population subgroup, utilized 15% of the aPAD. However, the acute exposure estimates for drinking water only for the most highly-exposed population subgroups (infants and children ages 1-2) exceed 100% of the aPAD at the 95th percentile of exposure (> 140% of the aPAD).

9.2 Steady State Aggregate Risk

Because there are no residential uses for diazinon, the steady state aggregate assessment includes dietary (food and water) exposures only. See Section 5.4. The steady state aggregate dietary (food and water) exposures and risk estimates for the registered uses of diazinon are of concern. The steady state (food only) exposure estimates are not of concern (did not exceed 100% of the aPAD). Food exposures for children 1-2 years old, the most highly exposed population subgroup, utilized 100% of the ssPAD. However, the steady state exposure estimates for drinking water only for the most highly-exposed population subgroups (infants and children ages 1-2) exceed 100% of the ssPAD at the 95th percentile of exposure (> 1400% of the ssPAD).

9.3 Cancer Aggregate Risk

Diazinon is classified as a "not likely to be carcinogenic to humans." Therefore, a quantitative cancer aggregate risk assessment is not required.

10.0 Cumulative Risk Characterization/Assessment

OPs, like diazinon, share the ability to inhibit AChE through phosphorylation of the serine residue on the enzyme leading to accumulation of acetylcholine and ultimately cholinergic neurotoxicity. This shared MOA/AOP is the basis for the OP common mechanism grouping per OPP's Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity (USEPA, 1999). The 2002 and 2006 CRAs used brain AChE inhibition in female rats as the source of dose response data for the relative potency factors and PoDs for each OP, including diazinon. Prior to the completion of Registration Review, OPP will update the OP CRA on AChE inhibition to incorporate new toxicity and exposure information available since 2006.

As described in Section 4.5, OPP has retained the FQPA Safety Factor for OPs, including diazinon, due to uncertainties associated with neurodevelopmental effects in children and exposure to OPs. There is a lack of an established MOA/AOP for the neurodevelopment outcomes which precludes the agency from formally establishing a common mechanism group per the Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity (USEPA, 1999) based on that outcome. Moreover, the lack of a recognized MOA/AOP and other uncertainties with exposure assessment in the epidemiology studies prevent the agency from establishing a causal relationship between OP exposure and neurodevelopmental outcomes. The Agency will continue to evaluate the epidemiology studies associated with neurodevelopmental outcomes and OP exposure prior to the release of the revised PRA. During this period, the Agency will determine whether or not it is appropriate to apply the draft guidance document entitled, Pesticide Cumulative Risk Assessment: Framework for Screening Analysis for the neurodevelopment outcomes.

11.0 Occupational Exposure/Risk Characterization

ORE memo: S. Tadayon, 6/10/2016, D426969.

The dermal and inhalation routes of exposure are assessed using route-specific toxicity studies. The occupational scenarios are expected to result in steady state exposures. The steady state approach is appropriate for diazinon given the toxicological and exposure profile. The steady state endpoint selection for diazinon overlaps with HED's traditional short-term exposure duration endpoint selection, as well as being appropriately health protective for workers that are exposed over longer periods of time (i.e., intermediate-term exposures).

For adults, when an endpoint is not sex-specific (i.e., the endpoints are based on developmental or fetal effects), a body weight of 80 kg is typically used in risk assessment; however, in this case, a female-specific body weight of 69 kg was used. While the endpoint of concern, AChE inhibition, is not sex-specific, the female-specific body weight was used to protect for pregnant women due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4).

11.1 Steady State Handler Risk

HED uses the term "handlers" to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the registered uses of diazinon. Exposure anticipated to be diazinon only. The quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios:

- Mixing/Loading Liquids for Aerial Applications
- Mixing/Loading Liquids for Airblast Applications
- Mixing/Loading Liquids for Chemigation
- Mixing/Loading Liquids for Groundboom Applications
- Mixing/loading Wettable Powder in Water Soluble Packaging to support Groundboom Application
- Mixing/loading Wettable Powder in Water Soluble Packaging to support Airblast Application
- Mixing/loading Wettable Powder in Water Soluble Packaging to support Aerial Application
- Mixing/loading Wettable Powder in Water Soluble Packaging to support Chemigation Application
- Applying Sprays for Aerial Applications
- Applying Sprays for Groundboom Applications

- Applying Sprays for Airblast Applications
- Flagger Sprays for Aerial Applications
- Mixing/Loading/Applying Liquids for Backpack Applications
- Mixing/Loading/Applying Liquids for Manually-Pressurized Handwand Applications
- Mixing/Loading/Applying Liquids for Mechanically-Pressurized Handgun Applications
- Mixing/Loading/Applying Wettable Powders in Water Soluble Bags for Backpack Applications
- Mixing/Loading/Applying Wettable Powders in Water Soluble Bags for Manually-Pressurized Handwand Applications
- Mixing/Loading/Applying Wettable Powders in Water Soluble Bags for Mechanically-Pressurized Handgun Applications

The above exposure scenarios best represent the registered use pattern for diazinon.

HED has no specific data developed to represent ear tag treatment use; the exposure and risk associated with animal ear tag use (occupational handler and/or post-application exposure) will not be higher than the quantitatively assessed exposure scenarios addressed below. Therefore, HED did not quantitatively assess the exposure and risk associated with the ear tag treatment use.

Occupational Handler Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. Assumptions and factors, as well as algorithms used to estimate non-cancer exposure and dose for occupational handlers, are detailed in the most recent ORE memo (D426969).

Application Rate: Product labels indicate that diazinon can be used at a range of maximum single application rates of 0.5-4.0 lbs ai/A. See Appendix E for additional information. The occupational handler assessment was completed assuming the single maximum application rate; lower application rates result in correspondingly lower exposures (i.e., lower risk to handlers).

Unit Exposures: It is the policy of HED to use the best available data to assess handler exposure. Sources of generic handler data, used as surrogate data in the absence of chemical-specific data, include PHED 1.1, the AHETF database, the Outdoor Residential Exposure Task Force (ORETF) database, or other registrant-submitted occupational exposure studies. Some of these data are proprietary (e.g., AHETF data), and subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures", are outlined in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table[12]", which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at the Agency website[13].

[12] Available: http://www.epa.gov/opp00001/science/handler-exposure-table.pdf
[13] Available: http://www.epa.gov/pesticides/science/handler-exposure-data.html

Area Treated or Amount Handled: Based on HED ExpoSAC Policy 9.1, the amount treated or handled per day was assumed to be:

- 350 acres for aerial application to typical acreage crops,
- 200 acres for ground application to high acreage crops,
- 80 acres for ground application to typical acreage crops,
- 40 acres for airblast application to orchards,
- 350 acres for chemigation applications,
- 40 gallons for backpack and manually-pressurized handwand applications,
- 1000 gallons for mechanically-pressurized handgun.

For most agricultural uses, it is reasonable to believe that occupational handlers will not apply the same chemical every day for more than a one-month time frame; however, there may be a large agribusiness and/or commercial applicators who may apply a product over a period of weeks (e.g. completing multiple applications for multiple clients within a region).

Diazinon is registered to control foliage and soil insects and pests on a variety of agricultural crops. The available product labels indicate that the product can be used in multiple applications per season with a minimum 7 day retreatment interval.

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates

Combined (dermal + inhalation) occupational handler risk estimates are presented using the Total MOE approach. All occupational handler scenarios show combined dermal and inhalation risk estimates of concern with maximum feasible clothing and PPE [i.e., a double layer of clothing, gloves and organic vapor respirator (PF10)] or engineering controls. Of the evaluated exposure scenarios assuming use of maximum PPE and/or engineering controls, the lowest combined MOE is 4 (LOC =1000). The combined MOEs for occupational handler scenarios range from 4 to 870. See Table 11.1.1.

The Agency matches quantitative occupational exposure assessment with appropriate characterization of exposure potential. While HED presents quantitative risk estimates for human flaggers where appropriate, agricultural aviation has changed dramatically over the past two decades. According the 2012 National Agricultural Aviation Association (NAAA) survey of their membership, the use of GPS for swath guidance in agricultural aviation has grown steadily from the mid 1990's. Over the same time period, the use of human flaggers for aerial pesticide applications has decreased steadily from ~15% in the late 1990's to only 1% in the most recent (2012) NAAA survey. The Agency will continue to monitor all available information sources to best assess and characterize the exposure potential for human flaggers in agricultural aerial applications.

Table 11.1.1. Steady state Occupational Exposure and Risk Estimates for Diazinon.										
Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai)[1]/PPE	Inhalation Unit Exposure (µg/lb ai)[1]/PPE	Maximum Application Rate[2]	Area Treated or Amount Handled Daily[3]	Dermal		Inhalation		Total
						Dose (mg/kg/day)[4]	MOE[5]	Dose (mg/kg/day)[6]	MOE[7]	MOE[8] (LOC=1000)
Mixing/Loading Liquids										
Airblast	Orchard [a]	8.6 Eng. Control	0.083 Eng. Control	2	40	0.00997	300	0.000096	2,300	270
	Orchard [b]			3		0.0149	200	0.00014	1,500	180
Aerial	lettuce only			2	350	0.0872	34	0.00084	260	30
Chemigation	Field and Orchard crop, typical acreage [c]			4		0.174	17	0.0017	130	15
	Orchard crop, typical acreage [d]			3		0.131	23	0.0013	170	20
	Field and Orchard crop, typical acreage [e]			2		0.0872	34	0.00084	260	30
	Field crop, typical acreage [f]			1		0.0436	69	0.00042	520	61
	Field and Orchard crop, typical acreage [g]			0.5		0.0219	140	0.00021	1,000	120
Groundboom	Field-grown ornamental			1	40	0.00499	600	0.000048	4,600	530
	Nursery (ornamentals, vegetables, trees, container stock)			1	60	0.00748	400	0.000072	3,300	350
	Field crop, typical acreage [c]			4	80	0.0399	75	0.00039	570	66
	Field crop, typical acreage [d]			3		0.0299	100	0.00029	760	88
	Field crop, typical acreage [e]			2		0.02	150	0.00019	1,100	130
	Field crop, typical acreage [f]			1		0.00997	300	0.00096	2,300	270
	Field crop, typical acreage [g]			0.5	80	0.00499	600	0000049	4,600	530
Mixing/Loading Wettable Powders In Water Soluble Packaging										
Airblast	Orchard Crops [a]	9.8 Eng. Control	0.24 Eng. Control	2	40	0.0114	260	0.00028	790	200
	Orchard Crops [b]			3		0.0171	180	0.00042	530	130
Aerial	lettuce only			2	350	0.0944	30	0.0024	91	23

Table 11.1.1. Steady state Occupational Exposure and Risk Estimates for Diazinon.										
Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai)[1]/PPE	Inhalation Unit Exposure (µg/lb ai)[1]/PPE	Maximum Application Rate[2]	Area Treated or Amount Handled Daily[3]	Dermal		Inhalation		Total
						Dose (mg/kg/day)[4]	MOE[5]	Dose (mg/kg/day)[6]	MOE[7]	MOE[8] (LOC=1000)
Chemigation	Field and Orchard crop, typical acreage [c]			4		0.199	15	0.0049	45	11
	Field and Orchard crop, typical acreage [d]			3		0.149	20	0.0037	60	15
	Field and Orchard crop, typical acreage [e]			2		0.0994	30	0.0024	91	23
	Field crop, typical acreage [f]			1		0.0497	60	0.0012	180	45
	Field and Orchard crop, typical acreage [g]			0.5		0.0249	120	0.00061	360	90
Groundboom	Field-grown ornamental crops			1	40	0.00568	530	0.00014	1,600	400
	Nursery (ornamentals, vegetables, trees, container stock)			1	60	0.00852	350	0.00021	1,100	270
	Field crop, typical acreage [c]			4	80	0.0455	66	0.00111	200	50
	Field crop, typical acreage [d]			3		0.0341	88	0.00086	260	66
	Field crop, typical acreage [e]			2		0.0228	130	0.00056	390	98
	Field crop, typical acreage [f]			1		0.0114	260	0.00028	790	200
	Field crop, typical acreage [g]			0.5		0.00568	530	0.00014	1,600	400
Applying Sprays										
Aerial	lettuce only	2.08 Eng. Control	0.0049 Eng. Control	2	350	0.0212	140	0.00005	4,400	130
Airblast	Orchard Crops [a]	14.6 Eng. Control	0.068 Eng. Control	2	40	0.017	180	0.000079	2,800	170
	Orchard Crops [b]			3		0.0254	120	0.00012	1,900	110
Groundboom	Field-grown ornamental			1	40	0.00296	1,000	0.000025	8,800	860

Table 11.1.1. Steady state Occupational Exposure and Risk Estimates for Diazinon.										
Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai)[1]/PPE	Inhalation Unit Exposure (µg/lb ai)[1]/PPE	Maximum Application Rate[2]	Area Treated or Amount Handled Daily[3]	Dermal		Inhalation		Total
						Dose (mg/kg/day)[4]	MOE[5]	Dose (mg/kg/day)[6]	MOE[7]	MOE[8] (LOC=1000)
	Nursery (ornamentals, vegetables, trees, container stock)	5.1 Eng. Control	0.043 Eng. Control	1	60	0.00443	680	0.000037	5,900	590
	Field crop, typical acreage [c]			4	80	0.0236	130	0.0002	1,100	110
	Field crop, typical acreage [d]			3		0.0177	170	0.00015	1,500	150
	Field crop, typical acreage [e]			2		0.0118	250	0.000099	2,300	220
	Field crop, typical acreage [f]			1		0.00591	510	0.00005	4,400	440
	Field crop, typical acreage [g]			0.5		0.00296	1,000	0.000025	8,800	870
Flagger										
Flagger for Aerial application	Lettuce	10.6 DL/G	0.035 Resp (PF10)	2	350	0.108	28	0.000036	6200	28
Mixing/Loading/Appling Liquids and Water Soluble Packaging										
Backpack Application (Ground soil directed)	Orchard, Nursery (ornamentals, vegetables, trees, container stock)	4120 DL/G	0.258 PF5 Resp	0.04 lb ai/gal	40 gallons	0.0955	31	0.000006	18,000	31
Backpack Application (Broadcast foliar)		16,900 DL/G	6.9 PF10 Resp	0.04 lb ai/gal		0.391	8	0.00016	1,400	8
Manually – Pressurized Handwand Broadcast foliar)		365 DL/G	3 PF10 Resp	0.04 lb ai/gal		0.00846	350	0.00007	3,200	290

Table 11.1.1. Steady state Occupational Exposure and Risk Estimates for Diazinon.										
Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai)[1]/PPE	Inhalation Unit Exposure (µg/lb ai)[1]/PPE	Maximum Application Rate[2]	Area Treated or Amount Handled Daily[3]	Dermal		Inhalation		Total
						Dose (mg/kg/day)[4]	MOE[5]	Dose (mg/kg/day)[6]	MOE[7]	MOE[8] (LOC=1000)
Mechanically-Pressurized Handgun Drench soil, ground directed and foliar)		1360 DL	0.87 PF10 Resp	0.04 lb ai/gal	1000 Gallons	0.788	4	0.0005	440	4

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (September 2015); Level of mitigation: Maximum PPE (Double layer clothing, gloves, organic vapor (PF10) respirator) for handheld equipment, or Eng. Controls (EC; closed cockpit for aerial applications, and closed cab for groundboom and airblast applications.

2 Based on currently registered labels.

3 Exposure Science Advisory Council Policy #9.1.

4 Dermal Dose = Dermal Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A or gal/day) ÷ BW (69 kg).

5 Dermal MOE = Dermal NOAEL (3 mg/kg/day) ÷ Dermal Dose (mg/kg/day).

6 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A or gal/day) ÷ BW (69 kg).

7 Inhalation MOE = Inhalation NOAEL (0.22 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

8 Total MOE = 1 / [(1/Dermal MOE) + (1/Inhalation MOE)].

[a] Orchard Crops: Apricot, Blueberry, Boysenberry, Cane berry, Cherry, Fig, Filbert, Nectarine, Peach, Pear, Plum, Prune (2 lb ai/A).

[b] Orchard crop: Almond (3 lb ai/A)

[c] Field crops typical acreage: Apple, Apricot, Beans(All Types), Beets, Broccoli, Brussels Sprouts, Cabbage, Cane berries, Carrot, Cauliflower, Collard, Cranberry, Cucumber, Endive, Fig, Kale, Melons (all types), Mustard, Onion (all types), Peas, Pepper, potato, Prune, Radish, Rutabaga, Shallot, Spinach, Tomato, Turnip (4 lb ai/A).

[d] Field crops typical acreage: Almond (3 lb ai/A).

[e] Field crops typical acreage : Blackberry, Dewberry, Lettuce, Loganberry, Nectarine, Peach, Pear, Plum, Rasberry (2 lb ai/A).

[f] Field crops typical acreage Pineapple, Strawberry (1 lb ai/A).

[g] Field crops typical acreage: Blueberry, Water cress, Filbert, Ginseng (0.5 lb ai/A).

11.2 Occupational Post-application Exposure/Risk Estimates

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for post-application exposure.

11.2.1 Occupational Post-application Inhalation Exposure/Risk Estimates

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010[14]. The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis[15]. During Registration Review, the agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for diazinon.

In addition, the Agency is continuing to evaluate the available post-application inhalation exposure data generated by the Agricultural Reentry Task Force. Given these two efforts, the Agency will continue to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the agency's risk assessments.

11.2.2 Occupational Post-application Dermal Exposure/Risk Estimates

A series of assumptions and exposure factors served as the basis for completing the occupational post-application risk assessments. Assumptions and factors, as well as algorithms used to estimate non-cancer exposure and dose for occupational post-application workers are detailed in the most recent ORE memo (D426969).

Transfer Coefficients: It is the policy of HED to use the best available data to assess post-application exposure. Sources of generic post-application data, used as surrogate data in the absence of chemical-specific data, are derived from ARTF exposure monitoring studies, and, as proprietary data, are subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting post-application exposure that are used in this assessment,

[14] http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html
[15] http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219.

known as "transfer coefficients", are presented in the ExpoSAC Policy 3[16], which, along with additional information about the ARTF data, can be found at the Agency website[17]. The anticipated post-application activities and dermal transfer coefficients for diazinon are discussed in the most recent ORE memo (D426969).

Application Rate: The foliar application rates for diazinon on the available product labels range from 0.5 to 4 lbs ai/A, depending on the target pest. The occupational post-application assessment was conducted at the maximum single application rate (4 lbs ai/A).

Exposure Time: The average occupational workday is assumed to be 8 hours.

Dislodgeable Foliar Residues: Two dislodgeable foliar residue (DFR) studies were submitted by the registrant that address the dissipation of diazinon on cabbage and broccoli (MRID 40202902) and citrus (MRID 40466601). These studies have been reviewed by HED and found to be acceptable for risk assessment (D229848, 03/15/2000).

Although the citrus use is no longer supported by the registrant, the data generated in this study can be used as surrogates for other crops. Because of the absence of additional DFR data for the various other crops treated with diazinon, the available DFR data are used as surrogate residue values for other crops using best scientific judgement. Uncertainties are introduced into the assessment when crop-specific residues are used to estimate residues from other types of crops; however, it is believed to be more realistic than assuming a default initial residue value based on the application rate and an assumed dissipation rate per day.

Dermal exposure to the oxon on foliar surfaces from reentry into an outdoor environment (e.g., field crops and orchards) previously treated with diazinon is not anticipated and, therefore, has not been assessed. No occupational exposure studies (DFR) were identified that quantified the levels of oxon present in the environment. Further, as noted above in Section 5.4.1, the dietary exposure risk assessment conducted in support of registration review concludes the following, "all residues in food are assumed to be parent diazinon, since the diazoxon is not typically found in foods, in monitoring data, or crop field trials."

A summary of how the DFR data were used is summarized in Table 11.2.2.1 and discussed in the most recent ORE memo (D426969).

Data from the citrus study were used in the post-application assessment for deciduous tree fruit and nut crops. The citrus data (MRID 40466601) represent DFR levels obtained at an application rate of 1.0 lb ai/acre. The DFR residues ($\mu g/cm^2$) were adjusted to account for any differences in application rates for the registered crops.

Data from the cabbage study (MRID 40202902) were used for crops with an application rate ranging from 0.5 to 3 lb ai/acre. For application rates other than 0.5 lb ai/acre, the DFR levels ($\mu g/cm^2$) were adjusted to account for any differences in application rates.

[16] Available: http://www.epa.gov/pesticides/science/exposac_policy3.pdf
[17] Available: http://www.epa.gov/pesticides/science/post-app-exposure-data.html

Table 11.2.2.1. Summary of DFR Data Use in Occupational Post-application Assessment for Diazinon.		
Crop for which DFR data available	Locations included in study	Crop groups for which DFR data used as surrogate
Citrus	California	Tree nuts and deciduous trees
Cabbage	California	Berry, Vegetable cucurbit, Vegetable leafy, Vegetable stem/stalk

Occupational Post-application Non-Cancer Dermal Risk Estimates
The post-application exposure scenarios associated with the registered uses of diazinon are summarized in Table 11.2.2.2.

For both the orchard crops (using the citrus DFR data) and the field crops (using the cabbage DFR data), there are risks of concern for most of the high contact post-application activities associated with each crop (e.g., hand harvesting, handset irrigation, etc). Some crop/activity combinations do not reach an acceptable MOE (LOC = 1000) until 8 days after application.

Table 11.2.2.2. Summary of Occupational/Commercial Post-application Risk Estimates for Diazinon.						
Crops	**Policy Crop Group Category**	**Max Foliar Rate (lb ai/acre)**	**Activities with Maximum Transfer Co-efficients (cm^2/hr)**	**High End exposure Activity**	**Dermal Dose (mg/kg/day)[a] [Day 0]**	**Days After Treatment Target MOE (1000) Achieved [b]**
Pineapple	Vegetable, Stem/Stalk	1	1100	Hand Harvesting	0.003	5 MOE=1,200)
Blackberries Raspberries, Blueberries,	Low Berry	0.5	1900	Irrigation (hand set)	0.002	8 (MOE=1,400)
Cranberries		3	1100	Scouting	0.002	7 (MOE=1,400)
Strawberries		1	1100	Hand Harvesting	0.003	5 (MOE=1200)
Apples, Apricots, Cherries, , Nectarines, Peaches, Pears, Plums	Deciduous tree fruit	2	3600	Thinning	0.002	8 (MOE=1700)
Fig		0.5			0.002	5 (MOE=1300)
Hazelnut (almonds dormant only)	Tree nuts	0.5	580	Scouting	0.002	2 (MOE=1,700)
Lettuce	Leafy Vegetable	0.5		Irrigation (hand set)	0.002	5 (MOE=1,400)

Table 11.2.2.2. Summary of Occupational/Commercial Post-application Risk Estimates for Diazinon.						
Crops	**Policy Crop Group Category**	**Max Foliar Rate (lb ai/acre)**	**Activities with Maximum Transfer Co-efficients (cm^2/hr)**	**High End exposure Activity**	**Dermal Dose (mg/kg/day)[a] [Day 0]**	**Days After Treatment Target MOE (1000) Achieved [b]**
Melons	Cucurbit Vegetables	4	1900	Irrigation (hand set)	0.003	8 (MOE=1,100)
Tomato	Fruiting Vegetable	0.8	1100	Irrigation (hand set)	0.003	5 (MOE=1,100)

(a) Daily Dermal Dose = [DFR (µg/cm^2) × Transfer Coefficient × 0.001 mg/µg × 8 hrs/day] ÷ BW (69 kg).
(b) Short-term and intermediate-term dermal NOAEL = 3 mg/kg/day (1000 target MOE).

Restricted Entry Interval

Diazinon is classified as Toxicity Category III via the dermal route and for eye irritation and inhalation. It is not a skin sensitizer. Under 40 CFR 156.208 (c) (2), if the product contains only one active ingredient and is an organophosphate, the REI should be 48 hours, or 72 hours in areas where average rainfall is less than 25 inches per year. However, since post-application risk estimates were a concern for up to several days after application for most crop/activity combinations; HED is recommending that the REI be revised on the labels to address those concerns according to the summary presented in Table 11.2.2.3.

Table 11.2.2.3. Summary of Restricted Entry Intervals.		
Crop	Current REI on product labels (days)	HED recommended REI (days)
Almond	7	NA(dormant only)
Pineapple	4	5
Blackberries Raspberries, Blueberries,	5	8
Cranberries	4	7
Strawberries	3	5
Apples, Apricots, Cherries, , Nectarines, Peaches, Pears, Plums	4	8
Fig	4	5
Hazelnut	18	2
lettuce	3	5
Melons	8	5
Tomato	2	5

HED recommends a minimum REI of 48 hours (72 hours in arid regions) for the product labels to be protective of the acute toxicity of diazinon.

12.0 Incident/Epidemiology Report

Incident Report memo: S. Recore, *et al*, 5/18/2016, D426971.

One component of the Agency's registration review program is consideration of human observational information including incident data, medical case reports, general medical information, and epidemiology studies. In conjunction with a human health risk assessment based on other data sources, such human incident and other human data can assist the Agency in better defining and characterizing the risk of pesticides/pesticide products.

Prior to 2000, diazinon was one of the most widely used insecticides available on the residential market. In 2000, based on potential risks to children identified during the reregistration process, all residential use diazinon products were cancelled. Sales of all indoor residential use products ended in 2002, and sales of all outdoor residential use products ended in 2004. The potential risks to occupational workers were also identified and subsequently mitigated via increased restricted entry intervals (REIs), prohibition of foliar application on most vegetables and elimination of aerial application and granular uses. Additionally, engineering controls were also required. The expected impacts of the Agency's regulatory decisions are generally reflected in the decrease of diazinon incidents over time across the four human incident databases analyzed: IDS (2003 to 2013), NPIC (2001 to 2012), PISP (2005 to 2010), and SENSOR-Pesticides (1998 to 2010).

The diazinon incident trends over time, in the analyzed databases, shows a decrease of diazinon incidents reflecting the cancellations. However, despite the cancellation of all residential uses some residential incidents are still occurring. Generally these incidents involve the use of cancelled product that users have had stored in their homes. In most cases these incidents involved homeowner/landlord applicator exposures and postapplication exposures. In addition, there were also several cases of individuals being exposed because of leaky containers stored in their homes or garages.

HED found that the health effects reported to the incident databases queried suggest that acute health effects of diazinon are typical of OP toxicity and include neurological (such as headaches and dizziness), gastrointestinal and respiratory effects, primarily. HED did not identify any aberrant effects outside of those anticipated and documented as a result of general OP toxicity. The OP-related effects are generally mild to moderate and resolve rapidly or are reversible with primary medical intervention.

The review of medical literature including medical case reports for diazinon poisonings found that like other organophosphates, diazinon can inhibit AChE enzyme causing increased level of the neurotransmitter acetylcholine at cholinergic synaptic and neuromuscular junctions which initiates toxic signs and symptoms. Aside from AChE inhibition, diazinon can cause airway hyperreactivity by acting on M2 muscarinic receptors on the airway smooth muscles (Lein P.J. and Fryer A.D., 2005). Inside the brain diazinon can increase the oxidative stress besides inhibiting the AChE (Pizzurro, 2013). Lee H.S., (1989), Dagli (1981), Venugopal L., et al., (2013) reported that diazinon poisoning can cause acute pancreatitis. Kidney failure and development of amorphous crystalluria due to diazinon poisoning was reported by Rubio (2012) and Wedin (1984). Medical case reports of accidental exposures in Spain (2009, 2012) and Egypt (2012) indicates that diazinon was used in residential (indoor) settings, and even applying for the head lice in those countries leading to acute poisonings. For the occupational use of

diazinon, the applicators should be aware that during improper storage, diazinon can often undergoes degradation and transforms into products that are more highly toxic than diazinon.

HED reviewed several dozen occupational and environmental epidemiological investigations of the potential role for diazinon, among other compounds, in the etiology of several cancer and non-cancer health outcomes. Investigations of the development of prostate, breast, colorectal, pancreatic, or pediatric cancers or glioma or cutaneous melanoma did not observe a positive association with exposure to diazinon. There is insufficient evidence of an association of diazinon with lung cancer and lymphoma. One study reported a significant, positive association with soft tissue sarcoma; however, these data must be replicated to better inform causal inference.

Regarding non-cancer outcomes, observations of an association with adverse neurodevelopmental outcomes among children exposed to diazinon during gestation are being evaluated in a separate effort within HED. Several studies indicate a possible role for diazinon, and organophosphate pesticides overall, in the etiology of respiratory effects including rhinitis, bronchitis, and wheeze. These data are within the AHS, although generally cross-sectionally evaluated; requiring additional study at this time. Other non-cancer health outcomes such as Parkinson's disease, diabetes, neurological effects, myocardial infarction, retinal degeneration, thyroid disease, and mental hygiene (suicide, depression) show little to no relationship to diazinon exposure in the current database.

13.0 Referenced Memoranda

D. Drew, 12/1/2000, DIAZINON. Revised HED Product and Residue Chemistry Chapter, D270422.

D. Drew, 4/22/2014, Diazinon: Registrant Response to Residue Chemistry Requirements (for Blueberries, Celery, Spinach, and Swiss chard) from the 2004 Interim Reregistration Eligibility Decision (IRED), D419217.

D. Drew, 5/3/2016, Diazinon Acute and Steady State Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments to Support Registration Review, D426970.

S. Recore, *et al*, 5/18/2016, Diazinon: Tier II Incident and Epidemiology Report, D426971.

K. White, 6/1/2016, Diazinon Registration Review Drinking Water Assessment, D418979.

S. Tadayon, 6/10/2016, Diazinon. Occupational and Residential Exposure Assessment for the Registration Review Risk Assessment, D426969.

Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for food use for diazinon are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Study	Technical	
	Required	**Satisfied**
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Acute Eye Irritation	yes	yes
870.2500 Acute Dermal Irritation	yes	yes
870.2600 Skin Sensitization	yes	yes
870.3100 90-Day Oral Toxicity in Rodents	yes	yes
870.3150 90-Day Oral Toxicity in Non-rodents	yes	yes
870.3200 21/28-Day Dermal Toxicity	yes	yes
870.3250 90-Day Dermal Toxicity	yes	yes
870.3465 90-Day Inhalation Toxicity	yes	yes [a]
870.3700a Prenatal Developmental Toxicity in Rodents	yes	yes
870.3700b Prenatal Developmental Toxicity in Non-rodents	yes	yes
870.3800 Reproduction and Fertility Effects	yes	yes
870.4100a Chronic Toxicity in Rodents	yes	yes
870.4100b Chronic Toxicity in Non-rodents	yes	yes
870.4200a Carcinogenicity in Rats	yes	yes
870.4200b Carcinogenicity in Mice	yes	yes
870.5100 Mutagenicity—Bacterial Reverse Mutation Test	yes	yes
870.5300 Mutagenicity—Mammalian Cell Gene Mutation Test	yes	yes
870.5375 Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5385 Mutagenicity—Mammalian Bone Marrow Chromosomal Aberration Test	yes	yes
870.5395 Mutagenicity—Mammalian Erythrocyte Micronucleus Test	yes	yes
870.6100 28-Day Delayed Neurotoxicity in Hens	yes	yes
870.6200a Acute Neurotoxicity Screening Battery in Rats	yes	yes
870.6200b 90-Day Neurotoxicity Screening Battery in Rats	yes	yes
870.6300 Developmental Neurotoxicity	yes	yes
Special Studies		
Comparative Cholinesterase in Rats	yes	yes [b]

[a] A 21-day study was considered adequate.

[b] A comparative cholinesterase assay was submitted with acute and repeated-dose data, but without gestational testing. However, as a DNT study was also submitted the gestational CCA is not required.

A.2 Toxicity Profiles

Summary of OPP's AChE Policy & Use of BMD Modeling

OPP's AChE policy (USEPA, 2000[18]) describes the manner in which AChE data are used in human health risk assessment. The following text provides a brief summary of that document to provide context to points of departure selected.

AChEI can be inhibited in the central or peripheral nervous tissue. Measurements of AChE or ChE inhibition in peripheral tissues (e.g., liver, diaphragm, heart, lung, etc.) are rare. Experimental laboratory studies generally measure brain (central) and blood (plasma and RBC) ChE. Blood measures do not represent the target tissue, but are instead used as surrogate measures for peripheral toxicity in studies with laboratory animals or for peripheral and/or central toxicity in humans. In addition, RBC measures represent AChE, whereas plasma measures are predominately butyryl-ChE (BuChE). RBC AChE data is expected to provide a better representation of the inhibition of AChE in target tissues. As part of the dose response assessment, evaluations of neurobehavior and clinical signs are performed to consider the dose response linkage between ChEI and apical outcomes.

Refinements to OPP's use of ChE data have come in the implementation of BMD approaches in dose response assessment. Beginning with the OP CRA, OPP has increased its use of BMD modeling to derive PODs for AChE inhibiting compounds. Most often, the decreasing exponential empirical model has been used.

OPP does not have a defined benchmark response (BMR) for OPs. However, the 10% level has been used in the majority of dose response analyses conducted to date. This 10% level represents a 10% reduction in AChE activity (i.e., inhibition) compared to background (i.e., controls). Specifically, the BMD_{10} is the estimated dose where ChE is inhibited by 10% compared to background. The $BMDL_{10}$ is the lower confidence bound on the BMD_{10}.

The use of the 10% BMR is derived from a combination of statistical and biological considerations. A power analysis was conducted by the Office of Research and Development (ORD) on over 100 brain AChE datasets across more than 25 OPs as part of the OP CRA (USEPA, 2002). This analysis demonstrated that 10% is a level that can be reliably measured in the majority of rat toxicity studies. In addition, the 10% level is generally at or near the limit of sensitivity for discerning a statistically significant decrease in ChE activity in the brain compartment and is a response level close to the background brain ChE level. With respect to biological considerations, a change in 10% brain ChEI is protective for downstream clinical signs and apical neurotoxic outcomes. With respect to RBC ChEI, these data tend to be more variable than brain AChE data. OPP begins its BMD analyses using the 10% BMR for RBC ChEI, but BMRs up to 20% could be considered on a case by case basis as long as such PODs are protective for brain ChEI, potential peripheral inhibition, and clinical signs of neurotoxicity.

[18] USEPA (2000) Office of Pesticide Programs, US Environmental Protection Agency, Washington DC 20460. August 18, 2000 Office of Pesticide Programs Science Policy of The Use of Data on Cholinesterase Inhibition for Risk Assessments of Organophosphorous and Carbamate Pesticides.

The results of the BMD modeling for the parent, diazinon, are as follows:

Table A.2.1. Results of BMD Modeling (mg/kg) for Brain and RBC ChE Data on Diazinon, Acute Oral Dosing Studies in Rats.					
Test	**Age Sex**	**Brain BMD_{10}**	**Brain $BMDL_{10}$**	**RBC BMD_{10}**	**RBC $BMDL_{10}$**
MRID 46166301 Acute CCA	Adult Male	NF (30% at 300 mg/kg)		NF (18% at 30 mg/kg)	
MRID 46166301 Acute CCA	Adult Female	6.824	6.492	NF (no effects at high dose)	
MRID 46166301 Acute CCA	PND 11 Male	NF (9% at 3 mg/kg)		NF (11% at 10 mg/kg)	
MRID 46166301 Acute CCA	PND 11 Female	3.194	2.925	3.362	2.963
MRID 43132203 Acute TC (9 hours)	Adult Male	14.702 [b]	12.175	6.932	4.804
MRID 43132203 Acute TC (9 hours)	Adult Female	12.876 [b]	9.218	NF	
MRID 43132204 Acute Neurotoxicity	Adult Male	NE		4.146	1.823
MRID 43132204 Acute Neurotoxicity	Adult Female	NE		5.229	1.754

[a] Hill model allowed the best fit.
[b] Value for the brain cortex.
CCA = Comparative Cholinesterase Assay
Acute TC = Time course for ChE inhibition following a single dose
NF = no model fit
NE = Not evaluated with BMD analysis, due to obvious lack of dose response

Table A.2.2. Results of BMD Modeling (mg/kg/day) for Brain and RBC ChE Data on Diazinon, Repeated Oral Dosing Studies in Rats.					
Test (dosing days)	**Age Sex**	**Brain BMD_{10}**	**Brain $BMDL_{10}$**	**RBC BMD_{10}**	**RBC $BMDL_{10}$**
MRID 46166302 Repeated Dose CCA (7)	Adult Male	23.639	19.625	2.339	0.284
MRID 46166302 Repeated Dose CCA (7)	Adult Female	3.425	3.118	NF (26% at 100 mg/kg)	
MRID 46166302 Repeated Dose CCA (7)	PND 11 Male	NF (22% at 3 mg/kg)		3.066	2.942
MRID 46166302 Repeated Dose CCA (7)	PND 11 Female	2.759	1.255	0.524	0.351
MRID 40815003 13-Week Oral Tox (87)	Adult Male	24.668	21.998	3.408	0.210
MRID 40815003 13-Week Oral Tox (87)	Adult Female	2.868	2.572	0.221	0.166
MRID 43543902 Subchronic NT (Week 13)	Adult Male	12.405 [b]	4.644	NF	
MRID 43543902 Subchronic NT (Week 13)	Adult Female	1.306 [b]	1.103	0.183	0.139
MRID 45842601	Adult	1.242	1.057	NF	

Table A.2.2. Results of BMD Modeling (mg/kg/day) for Brain and RBC ChE Data on Diazinon, Repeated Oral Dosing Studies in Rats.					
Test (dosing days)	**Age Sex**	**Brain BMD_{10}**	**Brain $BMDL_{10}$**	**RBC BMD_{10}**	**RBC $BMDL_{10}$**
RF DNT (21)	Female (Dam)				
MRID 45842602 RF DNT (15)	Adult Female (Dam)	1.648	1.175	0.123	0.123
MRID 45842602 RF DNT	Fetus Male	0.957	0.468	1.687	1.223
MRID 45842602 RF DNT	Fetus Female	11.552	7.996	16.605	1.701
MRID 46195601[a] DNT (16)	Adult Female (Dam)	1.429	1.246	NF (87% at 2.36 mg/kg)	
MRID 46195601[a] DNT	Pup Male (PND 4[c])	24.324	16.672	8.751	6.420
MRID 46195601[a] DNT	Pup Female (PND 4[c])	NE[d] (44.2% at 24.2 mg/kg)		NE[d] (37.8% at 24.2 mg/kg)	

[a] Hill model allowed the best fit.
[b] Value for the brain cortex.
[c] Only PND 4 (not PND 21) pups were evaluated with BMD analysis.
[d] No inhibition except at the high dose.
RF = Range finder
DNT = Developmental neurotoxicity test
CCA = comparative cholinesterase assay
NF = no model fit
NE = Not evaluated with BMD analysis

Table A.2.3. Results of BMD Modeling (mg/kg/day) for Brain and RBC ChE Data on Diazinon, Oral Toxicity in Dogs.					
Test (dosing days)	**Age Sex**	**Brain BMD_{10}**	**Brain $BMDL_{10}$**	**RBC BMD_{10}**	**RBC $BMDL_{10}$**
MRID 40815004 13-Week Oral Tox (92)	Adult Male	1.425	0.892	NT	
MRID 40815004 13-Week Oral Tox (92)	Adult Female	1.369	1.089	NT	
MRID 40815004 13-Week Oral Tox (86)	Adult Male	NT		NF	
MRID 40815004 13-Week Oral Tox (86)	Adult Female	NT		NE[a]	
MRID 40815004 13-Week Oral Tox (56)	Adult Male	NT		1.416	1.029

MRID 40815004 13-Week Oral Tox (56)	Adult Female	NT	0.992	0.786

[a] No dose response: 3075 mU/mL for control and low dose, 2950 mU/mL for mid-dose, and 2125 mU/mL for the two highest doses (0, 0.1, 0.5, 150 and 300 ppm).
NT = Cholinesterase Inhibition Not tested in the study
NE = Not evaluated with BMD analysis

Table A.2.4. Results of BMD Modeling (mg/kg/day) for Brain and RBC ChE Data on Diazinon, Dermal Toxicity in Rats.

Test (dosing days)	Age Sex	Brain BMD_{10}	Brain $BMDL_{10}$	RBC BMD_{10}	RBC $BMDL_{10}$
MRID 48497201 13-Week Dermal Tox (Week 13)	Adult Male	NF (10% at 25 mg/kg/day)		NF (No AChEi observed at highest dose tested)	
MRID 48497201 13-Week Dermal Tox (Week 13)	Adult Female	NF		0.077	0.068
MRID 46903001 4-Week Dermal Tox (Week 4)	Adult Male	NE		218.095 [a]	182.572
MRID 46903001 4-Week Dermal Tox (Week 4)	Adult Female	NE		469.587	388.799
MRID 46903001 4-Week Dermal Tox (Week 2)	Adult Male	NE		221.358 [a]	183.398
MRID 46903001 4-Week Dermal Tox (Week 2)	Adult Female	NE		371.930	345.433

[a] Hill model allowed the best fit.
NF = no model fit
NE = Not evaluated with BMD analysis, because RBC ChE inhibition is more sensitive than brain ChE inhibition.

Table A.2.5. Results of BMD Modeling (mg/L/day) for Brain and RBC ChE Data on Diazinon, Inhalation Toxicity in Rats. [a]

Test (dosing days)	Age Sex	Brain BMD_{10}	Brain $BMDL_{10}$	RBC BMD_{10}	RBC $BMDL_{10}$
MRID 41557402 21-Day Inhalation Tox (21)	Adult Male	NE		0.00236	0.00183
MRID 41557402 21-Day Inhalation Tox (21)	Adult Female	NF		0.00099	0.00082

[a] Exposure was nose-only for 6 hours each day for 7 consecutive days.
NE = Not evaluated with BMD analysis, due to obvious lack of dose response
NF = no fit; models did not adequately describe the data

The results of the BMD modeling for the oxon, <u>diazoxon</u>, are as follows:

Table A.2.6. Results of BMD Modeling (mg/kg) for Brain and RBC ChE Data on Diazoxon, Acute Oral Dosing Studies in Rats.					
Test	**Age Sex**	**Brain BMD_{10}**	**Brain $BMDL_{10}$**	**RBC BMD_{10}**	**RBC $BMDL_{10}$**
MRID 48663504 Acute CCA	Adult Male	NE [b]		0.234 [a]	0.168
MRID 48663504 Acute CCA	Adult Female	NE [b]		0.371 [a]	0.280
MRID 48663504 Acute CCA	PND 11 Male	NE [c] (20% at 5 mg/kg)		NF	
MRID 48663504 Acute CCA	PND 11 Female	NE [c]		0.275	0.237
MRID 48663501 RF Acute CCA	Adult Male	NE [d]		NE [d]	
MRID 48663501 RF Acute CCA	Adult Female	NE [d]		NE [d]	
MRID 48663501 RF Acute CCA	PND 11 Male	7.608	6.592	0.177 [a]	0.115
MRID 48663501 RF Acute CCA	PND 11 Female	7.909	6.929	0.300 [a]	0.188

[a] Hill model allowed the best fit.
[b] No dose response
[c] RBC ChE inhibition is more sensitive than brain ChE inhibition.
[d] n=2
CCA = Comparative Cholinesterase Assay
NF = no model fit
NE = Not evaluated with benchmark modeling

Table A.2.7. Results of BMD Modeling (mg/kg/day) for Brain and RBC ChE Data on Diazoxon, Repeated Oral Dosing Studies in Rats.					
Test (dosing days)	**Age Sex**	**Brain BMD_{10}**	**Brain $BMDL_{10}$**	**RBC BMD_{10}**	**RBC $BMDL_{10}$**
MRID 48663505 Repeated Dose CCA (7)	Adult Male	NDR		0.260	0.196
MRID 48663505 Repeated Dose CCA (7)	Adult Female	NE [a]		0.220 [b]	0.114
MRID 48663505 Repeated Dose CCA (7)	PND 11 Male	2.232	1.786	NF	
MRID 48663505 Repeated Dose CCA (7)	PND 11 Female	4.567	1.079	NF	
MRID 48663501 RF Repeated Dose CCA (7)	Adult Male	NE [c]		NE [c]	
MRID 48663501 RF Repeated Dose CCA (7)	Adult Female	NE [c]		NE [c]	
MRID 48663501 RF Repeated Dose CCA (7)	PND 11 Male	NE [d]		NF	
MRID 48663501 RF Repeated Dose CCA (7)	PND 11 Female	5.142	3.521	0.332	0.266

[a] 10% inhibition was not observed

[b] Hill model allowed the best fit.
[c] n=2
[d] RBC ChE inhibition is more sensitive than brain ChE inhibition.
CCA = comparative cholinesterase assay
NDR = No dose response
NE = Not evaluated with BMD analysis
NF = no model fit

Diazinon Toxicity Profiles follow (only select studies shown; not all-inclusive):

Table A.2.8. Acute Toxicity Profile - Diazinon

Guideline No.	Study Type	MRID #	Results	Toxicity Category
870.1100	Acute oral [rat]	41407218	LD_{50} = 1340 mg/kg (♂) LD_{50} = 1160 mg/kg (♀)	III
870.1200	Acute dermal [rabbit]	41407219	$LD_{50} \geq$ 2020 mg/kg	III
870.1300	Acute inhalation [rat]	41407220	LC_{50} > 2.33 mg/L/4 h	III
870.2400	Acute eye irritation [rabbit]	41407221	mild irritant	III
870.2500	Acute dermal irritation [rabbit]	41407222	mild irritant	III
870.2600	Dermal sensitization [guinea pig]	41407223 00232008	not a sensitizer	NA

Table A.2.9. Subchronic, Chronic, and Other Toxicity Profile - Diazinon and Diazoxon

Guideline No./Study Type	MRID No. (year)/ TXR #/ Classification /Doses	Results
870.3100a 90-Day oral toxicity rodents – rat	40815003 (1988) Acceptable, guideline ♂♀: 0, 0.5, 5, 250, 2500 ppm ♂: 0, 0.03, 0.3, 15, 168 mg/kg/day ♀: 0, 0.04, 0.4, 19, 212 mg/kg/day	NOAEL = 0.04 mg/kg/day LOAEL = 0.4 mg/kg/day based on decreased RBC AChE in females Systemically at 168 ♂/212 ♀ mg/kg/day, hypersensitivity to sound and touch, aggressiveness, deceased body weight, decreased feed consumption, decreased hemoglobin and hematocrit, increase liver weight (absolute and relative), and hepatocellular hypertrophy were observed. At 250 ppm, RBC AChE was inhibited in males and brain AChE was inhibited in females. At 2500 ppm brain AChE was inhibited in males.
870.3150 90-Day oral toxicity – dog	40815004 (1988) Acceptable, guideline ♂♀: 0, 0.1, 0.5, 150, 300 ppm ♂: 0, 0.0034, 0.020, 5.9, 10.9 mg/kg/day ♀: 0, 0.0037, 0.021, 5.6, 11.6 mg/kg/day	NOAEL = 0.020/0.0037 (♂/♀) mg/kg/day LOAEL = 5.9/5.6 mg/kg/day based on decreased RBC and brain AChE in both sexes Systemically, decreased BW was noted at 5.6 mg/kg/day.

Table A.2.9. Subchronic, Chronic, and Other Toxicity Profile - Diazinon and Diazoxon		
Guideline No./Study Type	**MRID No. (year)/ TXR #/ Classification /Doses**	**Results**
870.3200 21-Day dermal toxicity – rabbit	40660807 (1984) Acceptable, guideline ♂♀: 0, 1, 5, 100 mg/kg/day; 100 mg/kg/day reduced to 50 mg/kg/day on Day 7	NOAEL = 1 mg/kg/day LOAEL = 5 mg/kg/day based on decreased brain AChE in females Systemically, deaths related to cholinergic inhibition were noted at 100 mg/kg/day. At 50 mg/kg/day, decreased RBC and brain AChE were noted in both sexes.
870.3250 90-Day dermal toxicity – rat	48497201 (2011) Acceptable, non-guideline ♂♀: 0, 0.3, 1, 3, 25 (♂)/10 (♀) mg/kg bw/day	NOAEL = 3 mg/kg/day LOAEL = 10 mg/kg/day based on decreased brain and RBC AChE in females. No inhibition observed in males at 10 mg/kg/day. Systemically, no adverse effect was noted. At 25 mg/kg/day, decreased brain AChE were noted in males; decreased RBC AChE was not noted in males.
870.3465 90-Day inhalation toxicity – rat (this is a 21-day study which was considered acceptable for this chemical)	40815002 (1988) Acceptable, guideline ♂♀: 0, 0.1, 1, 10, 100 µg/L	NOAEL was not observed LOAEL = 0.1 µg/L based on decreased RBC AChE in males At 1 µg/L and above, decreased brain and RBC AChE was noted in both sexes.
870.3700a Prenatal developmental toxicity – rat	00153017 (1988) Acceptable, guideline ♀: 0, 10, 20, 100 mg/kg/day on GD 6-15	Maternal: NOAEL = 20 mg/kg/day LOAEL = 100 mg/kg/day based on ↓BWG Fetal: NOAEL = 100 mg/kg/day LOAEL was not observed
870.3700b Prenatal developmental toxicity – rabbit	00079017 (1981) Acceptable, guideline ♀: 0, 7, 25, 100 mg/kg/day on GD 6-18	Maternal: NOAEL = 25 mg/kg/day LOAEL = 100 mg/kg/day based on deaths with tremors and convulsions, ↓BWG, and gastro-intestinal hemorrhages and erosions Fetal: NOAEL = 100 mg/kg/day LOAEL was not observed

Table A.2.9. Subchronic, Chronic, and Other Toxicity Profile - Diazinon and Diazoxon		
Guideline No./Study Type	**MRID No. (year)/ TXR #/ Classification /Doses**	**Results**
870.3800 Reproduction and fertility effects – rat	41158101 (1989) Acceptable, guideline ♂♀: 0, 10, 100, 500 ppm ♂: 0, 0.67, 6.69, 35.15 mg/kg/day ♀: 0, 0.77, 7.63, 41.43 mg/kg/day	Parental: NOAEL = 0.67 ♂/ 0.77 ♀ mg/kg/day LOAEL = 6.69 ♂/ 7.63 ♀ mg/kg/day based on ↓BWG Offspring: NOAEL = 0.67 ♂/ 0.77 ♀ mg/kg/day LOAEL = 6.69 ♂/ 7.63 ♀ mg/kg/day based on ↓BWG and pup mortality Reproduction: NOAEL = 6.69 ♂/ 7.63 ♀ mg/kg/day LOAEL = 35 ♂/41 ♀ mg/kg/day based on decreased male and female mating and fertility indices (second parental group) and increased gestation length At 41 mg/kg/day, tremors in females.
870.4100b Chronic toxicity – dog	41942001 (1991) Acceptable, guideline ♂♀: 0, 0.1, 0.5, 150, 300 ppm (reduced after 14 weeks to 225 ppm) ♂: 0, 0.0032, 0.015, 4.7, 7.7 mg/kg/day ♀: 0, 0.0037, 0.020, 4.5, 9.1 mg/kg/day	NOAEL = 0.015 ♂/0.020 ♀ mg/kg/day LOAEL = 4.7 ♂/4.5♀ mg/kg/day based on decreased brain and RBC AChE in both sexes, ↓BWG, ↓FC, ↑serum amylase
870.4200a Carcinogenicity – rat	00073372 (19??) Acceptable, guideline ♂♀: 0, 400, 800 ppm ♂♀: 0, 20, 40 mg/kg/day	Systemic NOAEL = 40 mg/kg/day LOAEL was not observed (AChEI not measured) No evidence of carcinogenicity
870.4200b Carcinogenicity – mouse	00073372 (19??) Acceptable, guideline ♂♀: 0, 100, 200 ppm ♂♀: 0, 14, 29 mg/kg/day	Systemic NOAEL = 29 mg/kg/day LOAEL was not observed (AChEI not measured) No evidence of carcinogenicity
870.4300 Chronic toxicity/ carcinogenicity – rat	41942002 (1991) Acceptable, guideline ♂♀: 0, 0.1, 1.5, 125, 250 ppm ♂: 0, 0.004, 0.06, 5, 10 mg/kg/day ♀: 0, 0.005, 0.07, 6, 12 mg/kg/day	NOAEL = 0.06 ♂/0.07 ♀ mg/kg/day LOAEL = 5 ♂/6 ♀ mg/kg/day based on decreased brain and RBC AChE No systemic toxicity was observed. No evidence of carcinogenicity
Mutagenicity studies	7 studies are summarized in Appendix A.4. No mutagenicity was observed.	

Table A.2.9. Subchronic, Chronic, and Other Toxicity Profile - Diazinon and Diazoxon		
Guideline No./Study Type	**MRID No. (year)/ TXR #/ Classification /Doses**	**Results**
870.6200 Acute neurotoxicity screening battery – rat	43132201, 43132204 (1993) Acceptable, guideline ♂♀: 0, 2.5, 150, 300, 600 mg/kg/day	NOAEL = 2.5 mg/kg/day LOAEL = 150 mg/kg/day based mainly on abnormal gait, ↓ body temperature, ↓ rearing count, stereotypy (all in ♀); ↓ fecal consistency, stained fur in ♂; ↓ RBC AChE
870.6200 Subchronic neurotoxicity screening battery – rat	43549302, 43543901 (1994) Acceptable, guideline ♂♀: 0, 0.018, 1.8, 18, 180 mg/kg/day	NOAEL = 0.018 mg/kg/day LOAEL = 1.8 mg/kg/day based on reduced RBC AChE in both sexes and cerebral cortex/hippocampus AChE in females At 18 mg/kg/day, brain AChE was reduced in both sexes. At 180 mg/kg/day, ↓BWG, ↓FC, muscle fasciculation, 8/15 females; hyper-responsiveness and tremors, and decrease in grip strength.
870.6300 Developmental neurotoxicity – rat	46195601 (2003) Acceptable, non-guideline 0, 0.026, 2.36, 24.2 mg/kg/day (gestational period)	Maternal NOAEL = 0.026 mg/kg/day LOAEL = 2.36 mg/kg/day based on reduced RBC and brain AChE; no systemic toxicity was noted at the highest dose tested Offspring NOAEL = 0.026 mg/kg/day LOAEL = 2.36 mg/kg/day based on reduced RBC AChE in both sexes Offspring systemic toxicity: NOAEL = 2.36 mg/kg/day LOAEL = 24.2 mg/kg/day based reduced body weight and body weight gain and delayed sexual maturation in males and females Classified as non-guideline due to inadequacies in the assessment of motor activity in the offspring.
870.7485 Metabolism – rat	41108901 (1989)	After 24 hours most of the ^{14}C was recovered in the urine (58.2% and up to 93.3%) and smaller amounts (<2.5%) in the feces. After 7 days recovery was 96.7% to 100.25% and < 1% of the label remained in the tissues. The highest level was in the blood. Three major metabolites were identified in the urine to indicate that diazinon is metabolized to liberate the pyrimidinyl group that is oxidized and excreted. Only trace amounts of parent diazinon were present in the urine or feces.

Table A.2.9. Subchronic, Chronic, and Other Toxicity Profile - Diazinon and Diazoxon		
Guideline No./Study Type	**MRID No. (year)/ TXR #/ Classification /Doses**	**Results**
870.7800 Immunotoxicity – mouse	48694201 (2011) Acceptable, guideline ♀: 0, 32, 160, 800 ppm ♀: 0, 6, 32, 150 mg/kg/day ♀: 0, 400 ppm ♀: 0, 75 mg/kg/day	Immunotoxicity NOAEL = 75 mg/kg/day LOAEL was not established Systemic toxicity NOAEL = 32 mg/kg/day LOAEL = 75 mg/kg/day based on reduced body weights The second groups (0 and 400 ppm) were evaluated after the 800 ppm group was discontinued on Day 9 due to a large decrease in BW and water consumption.
Non-guideline Dermal absorption – human	44982801 (1999) Acceptable, non-guideline 2 µg/cm^2 on ventral forearm or abdomen 1.47 µg/cm^2 on abdomen	Adult human volunteers (6/ group) were dosed dermally with ^{14}C- Diazinon. The application site was washed with soap and water after 24 hours and tape stripped after 7 days. Total urine was collected for 7 days and analyzed for radiolabel. Five rhesus monkeys were dosed intravenously with ^{14}C-Diazinon and total urine and feces collected for 7 days. Urine and feces were analyzed for radiolabel. Rhesus urinary excretion of radiolabel (56%) was used to correct human urinary excretion of radiolabel as a measure of absorbed dose. Absorption was 2-4%.
Non-guideline ChEI – rat	43132203 (1994) Acceptable, non-guideline ♂♀: 0, 2.5, 150, 300, 600 mg/kg/day	Rats were sacrificed in groups of 5/sex after 3, 9, or 24 hours. These intervals were designated as pre-peak, peak, and post-peak for effects. The rats were assessed for clinical signs and for plasma ChE, RBC and brain AChE. Clinical signs were first evident in the 300 mg/kg dose group males at 9 hours and at 600 mg/kg at 3 hours. Males were more frequently affected than females. RBC AChE was inhibited in females dosed with 2.5 mg/kg and above. Brain AChE inhibition was noted at 150 mg/kg in all four regions of the brain examined and the spinal cord.
Non-guideline ChEI – rat	44219301 (1993) Acceptable, non-guideline Part 1, ♂♀: 0, 100, 250, 500 mg/kg ♀: 25, 50 mg/kg Part 2, ♂: 0, 0.05, 0.5, 1, 10, 100, 500 mg/kg ♀: 0, 0.05, 0.12, 0.25, 2.5, 25, 250 mg/kg	Part 1 (behavioral effects), The rats were observed for clinical signs for 14 days. At 100 mg/kg, females were noted to have one incident of hypoactivity. At 250 and/or 500 mg/kg, miosis, hypoactivity, fur staining, and/or loss of pain reflex occurred, and at 500 mg/kg there was one death. These findings were corroborated by the ChE/AChE part of the study which also demonstrated miosis at 100 mg/kg in a single male rat. The LOAEL is 250 mg/kg based on miosis and hypoactivity. The NOAEL is 100 mg/kg, but this is considered a threshold dose level. In Part 2 (ChE/AChE effects), Animals were sacrificed ~24 hours post-dose. Observations on their behavior reactions were noted, and the blood and brain were assessed for ChE/AChE. RBC AChE was inhibited at 25 mg/kg in females and at 100 mg/kg in males. Brain AChE was inhibited at 25 and 250 mg/kg in females and at 500 mg/kg in males. The LOAEL is 25 mg/kg based on RBC and brain AChE inhibition in females. The NOAEL is 2.5 mg/kg.

Table A.2.9. Subchronic, Chronic, and Other Toxicity Profile - Diazinon and Diazoxon		
Guideline No./Study Type	**MRID No. (year)/ TXR #/ Classification /Doses**	**Results**
Non-guideline ChEI – human	00091536 (1966) Unacceptable, non-guideline 0, 0.02, 0.025 mg/kg/day	Dosed by capsule for 38 or 43 days. Red blood cell acetyl cholinesterase was not inhibited. An audit carried out in 1980 (Clements report) classified this study as "INVALID" based on the following findings: 1) no physician oversight; 2) no rationale for the 'normalization' factor used in data reporting; 3) no analysis of capsules or record of specific dose administered; and 4) no raw data available.
Non-guideline Comparative cholinesterase assay of parent – rat	46166301, 46166302 (2003) Acceptable, non-guideline 8 rats/sex/dose were treated with a single gavage dose in corn oil at 0, 0.3, 3.0, 30, 300 mg/kg in the adults and 0, 0.3, 3.0, 10, 100 mg/kg/day in the PND 11 pups 8 rats/sex/dose were treated once daily for 7 consecutive days at 0, 0.03, 0.3, 10, 100 mg/kg/day in the adults and 0, 0.03, 0.3, 3, or 30 mg/kg/day in the PND 11 pups (at start). No gestational CCA submitted.	In the acute study, the LOAEL in adults was 30 mg/kg/day based on AChE inhibition in the RBC (♂) and brain (♀). The NOAEL was 3.0 mg/kg/day. The LOAEL in the PND 11 pups was 10 mg/kg/day based on AChE inhibition in the RBC (♀) and brain (♂♀). The NOAEL was 3.0 mg/kg/day. Systemically, tremors were first noted in adults at 30 mg/kg (♀) and PND 11 pups at 10 mg/kg (♀). In the repeated dose study, the LOAEL in adults was 10 mg/kg/day based on AChE inhibition in the RBC (♂) and brain (♀). The NOAEL was 0.3 mg/kg/day. The LOAEL in the PND 11 pups was 3 mg/kg/day based on AChE inhibition in the RBC (♀) and brain (♂♀). The NOAEL was 0.3 mg/kg/day. Systemically, tremors were noted in pups from all dose groups, and ↓ absolute brain weight in males at 3 mg/kg and above. Increased salivation was noted in 100 mg/kg adults..

Table A.2.9. Subchronic, Chronic, and Other Toxicity Profile - Diazinon and Diazoxon		
Guideline No./Study Type	**MRID No. (year)/ TXR #/ Classification /Doses**	**Results**
Non-guideline Comparative cholinesterase assay of **oxon** – rat	48663501 (2011) Acceptable, non-guideline Animals were treated with a single gavage dose at 0, 0.3, 30, 60, 100 mg/kg in the adults (2 rats/sex/dose) and 0, 3, 10, 20, 30 mg/kg/day in the PND 11 pups (8 rats/sex in controls and 3/sex/dose in other groups) Animals were treated once daily for 7 consecutive days at 0, 3, 30, 45 mg/kg/day in the adults and 0, 1, 3, 6, 10 mg/kg/day in the PND 11 pups. (same animal numbers as acute) No gestational CCA submitted.	In the acute study, the LOAEL in adults was 0.3 mg/kg/day based on AChE inhibition in the RBC (♂♀). The NOAEL was not observed. The LOAEL in the PND 11 pups was 3 mg/kg/day based on AChE inhibition in the RBC. The NOAEL was 0.3 mg/kg/day. Systemic effects in adults: All rats in the 60 or 100 mg/kg group were sacrificed between 40 minutes and approximately 2 hours post-dose due to deteriorating clinical condition. Clinical signs included piloerection, under-active behavior, uncoordinated and/or elevated gait, partially closed eyes, and reduced body tone. At these doses, marked inhibition of RBC AChE (but not brain AChE) was observed. Systemic effects in pups: unsteady gait, cold to touch, tremors, underactive behavior, flattened gait and gasping respiration were noted prior to mortality at 1 hour post-dose at 20 and 30 mg/kg/day. In the repeated dose study, the LOAEL in adults was 3 mg/kg/day based on AChE inhibition in the RBC (♂♀). The NOAEL was not observed. The LOAEL in the PND 11 pups was 1 mg/kg/day based on AChE inhibition in the RBC (♂♀). The NOAEL was not observed. Systemic effects in adults: All animals tolerated administration of diazoxon with no consistent clinical signs. Systemic effects in pups: tremors, underactive behavior, unsteady gait and splayed hindlimbs were noted prior to mortality at 10 mg/kg/day. .
Non-guideline Time to peak effect study of **oxon** – rat	48663503 (2011) Acceptable, non-guideline 15 rats/sex/dose were treated with a single gavage dose in corn oil at 0 or 45 mg/kg	3 rats/sex/dose were killed at 45 minutes, 90 minutes, 3 hours, 6 hours or 9 hours after dosing. It was concluded that arena observations demonstrated that the time to peak effects on behavior was 30 minutes post-dosing. On the other hand, the time to peak effects on AChE was 90 minutes post-dosing, based on the results of the AChE activity assessment, particularly the degree of inhibition of AChE observed in the erythrocytes. Consequently, the time to peak effects for young adult rats in this study was determined to be 1 hour post-dosing, in order to capture both behavioral and enzyme inhibition peaks.

Table A.2.9. Subchronic, Chronic, and Other Toxicity Profile - Diazinon and Diazoxon		
Guideline No./Study Type	**MRID No. (year)/ TXR #/ Classification /Doses**	**Results**
Non-guideline Acute comparative cholinesterase assay of **oxon** – rat	48663504 (2011) Acceptable, non-guideline 8 adult rats/sex/dose were treated with a single gavage dose in corn oil at 0, 0.2, 2, 10, or 45 mg/kg 8 PND 11 rats/sex/ dose were treated with a single gavage dose in corn oil at 0.2, 2, 5, or 10 mg/kg	Systemic effects. Adults: At 10 mg/kg treatment-related findings in one male included hunched posture, flattened gait, whole body tremor and piloerection. One female had flattened gait. At 45 mg/kg four males and two females were affected and demonstrated signs including reduced arousal, minor gait abnormalities (elevated or flattened), hunched posture, whole body tremor, piloerection, reduced activity and rearing scores and loose feces. Pups: There was no mortality. No consistent treatment related effects on arena parameters were observed. ChE Inhibition Adults: RBC AChE was decreased in all dose groups in both sexes. Brain AChE was not inhibited. Pups: RBC AChE was decreased in all dose groups in both sexes. Brain AChE was decreased at 5 and 10 mg/kg in males and 10 mg/kg in females.
Non-guideline Repeated-dose comparative cholinesterase assay of **oxon** – rat	48663505 (2011) Acceptable, non-guideline 8 adult rats/sex/dose and 8 PND 11 pups/sex/ dose were treated with daily gavage doses in corn oil at 0, 0.05, 0.1, 1, or 5 mg/kg/day for 7 consecutive days	Systemic effects: None noted in adults or pups. AChE Inhibition Adults: RBC AChE was decreased in the 1 and 5 mg/kg/day groups (both sexes). Brain AChE was not inhibited. Pups: RBC AChE was decreased in all dose groups in both sexes. Brain AChE was decreased at 5 mg/kg/day in both sexes.

A.3 Hazard Identification and Endpoint Selection

A.3.1 Acute Reference Dose (aRfD) - Females Age 13-49 and General Population

Study Selected: Acute Comparative Cholinesterase Assay in Rats
MRID No.: 46166301
Executive Summary: See Appendix A.4, Non-Guideline
Dose and Endpoint for Risk Assessment: $BMDL_{10}$ = 3.0 mg/kg/day based on RBC AChEI in the female PND 11 pups. The BMD_{10} was 3.4 mg/kg/day.
Comments about Study/Endpoint/Uncertainty Factors: RBC cholinesterase inhibition was selected as the endpoint for the POD, since BMD_{10} values were lower than those for brain cholinesterase inhibition. Data from the PND 11 pups are appropriate for acute POD derivation, since effects were observed after a single exposure and the endpoint is the most sensitive adverse response in all populations (infant and children, females 13+, and adults). An uncertainty factor of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation and FQPA/ database uncertainty factor) is applied to the $BMDL_{10}$ to obtain an aPAD (= aRfD) of 0.003 mg/kg. The FQPA/ database uncertainty factor of 10X is based on incorporating uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4); this factor may be excluded for the sub-population of adults 50-99.

A.3.2 Chronic (Steady State) Reference Dose (ssRfD)

Study Selected: Repeated-Dose Comparative Cholinesterase Assay in Rats
MRID No.: 46166302
Executive Summary: See Appendix A.4, Non-Guideline
Dose and Endpoint for Risk Assessment: $BMDL_{10}$ = 0.35 mg/kg/day based on RBC AChEI in the female PND 11 pups (at study initiation). The BMD_{10} was 0.52 mg/kg/day.
Comments about Study/Endpoint/Uncertainty Factors: RBC cholinesterase inhibition was selected as the endpoint for the POD, since BMD_{10} values were lower than those for brain cholinesterase inhibition. Of the best modeled data sets, data from the PND 11 pups provided the most sensitive adverse response in all populations (infant and children, females 13+, and adults). For diazinon, data suggests that steady state RBC AChEI has been reached within 7 days. The study was also selected because it had the best dose response and curve fit of the various repeat-dose studies available listed in Appendix Table 2.1. An uncertainty factor of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation and FQPA/ database uncertainty factor) is applied to the $BMDL_{10}$ to obtain an ssPAD (= ssRfD) of 0.00035 mg/kg. The FQPA/ database uncertainty factor of 10X is based on incorporating uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4); this factor may be excluded for the sub-population of adults 50-99.

A.3.3 Incidental Oral Exposure (Steady State)
Same as section A.3.2, allowing a Level of Concern (LOC) of 1000.

A.3.4 Dermal Exposure (Steady State)

Study Selected: 90-Day Dermal Toxicity Study in Rats

MRID No.: 48497201
Executive Summary: See Appendix A.4, Non-Guideline
Dose and Endpoint for Risk Assessment: NOAEL = 3.0 mg/kg/day based on RBC and brain AChEI in the adult females. The LOAEL was 10 mg/kg/day.
Comments about Study/Endpoint/Uncertainty Factors: Endpoint was the inhibition of RBC and brain ChE in adult female rat. It is noted that a visual examination of the graphical display of the BMD results indicated poor curve fits, so a NOAEL was used as the POD. The NOAEL in the male rat was 25.0 mg/kg/day, the highest dose tested, thus the female data is more protective. Although in this test, the NOAEL for brain AChEI was lower than for RBC AChEI in both sexes, RBC AChEI was most often the sensitive compartment in the entire diazinon toxicological database and was relied upon for endpoint selection. With a common endpoint of RBC AChEI, the most protective aggregate risk assessment is allowed. The route-specific study is preferred for risk assessment, and the full 10X FQPA (database) uncertainty factor is used to insure that the risk assessment is protective of children. A total uncertainty factor of 1000X is appropriate (10X for interspecies extrapolation, 10X for intraspecies variation, and 10X database uncertainty factor), allowing a LOC of 1000.

A.3.5 Inhalation Exposure (Steady State)

Study Selected: 21-Day Inhalation Toxicity Study
MRID No.: 41557402
Executive Summary: See Appendix A.4, Non-Guideline
Dose and Endpoint for Risk Assessment: $BMDL_{10}$ = 0.816 mg/m^3/day, based on RBC AChEI in the adult females. The BMD_{10} was 0.988 mg/mg^3/day.
Comments about Study/Endpoint/Uncertainty Factors: Endpoint was the inhibition of RBC AChE in the adult female rat. The route-specific study was used, rather than using an oral study with a route-to-route extrapolation and assuming similar toxicity between the two routes of exposure. Results from the female are protective of the male in this study. A total uncertainty factor of 1000X is appropriate (10X for interspecies extrapolation, 10X for intraspecies variation, and 10X database uncertainty factor), allowing a LOC of 1000.

A.4 Executive Summaries

A.4.1 Subchronic Toxicity

870.3100 90-Day Oral Toxicity – Rat

In a subchronic feeding study (MRID 40815003), 5 groups of 15/sex Sprague-Dawley strain rats were dosed as 0, 0.5, 5, 250 or 2500 ppm of diazinon MG-8 for 13 weeks. These doses correspond to 0.03/0.04, 0.3/0.4, 15/19 or 168/212 mg/kg/day of diazinon in rats. Systemic toxicity was evident in the 2500 ppm dose group only and consisted of hypersensitivity to sound and touch, aggressiveness, deceased body weight, decreased feed consumption, decreased hemoglobin and hematocrit, increase liver weight (absolute and relative), hepatocellular hypertrophy. The LOEL is 168 mg/kg/day. Based on several parameters including decreased body weight. The NOEL is 19 mg/kg/day. Plasma ChE was inhibited at 5 ppm in males

(26%) and females (78%, both $p < 0.01$) and RBC AChE was inhibited in females (17%, $p < 0.01$). At 250 ppm, RBC AChE was inhibited in males (27%, $p < 0.01$) and brain AChE was inhibited in females (41%, $p < 0.01$). At 2500 ppm brain AChE was inhibited in males (50%). The LOEL is 0.3 mg/kg/day based on plasma ChE and RBC AChE inhibition. The NOEL is 0.04 mg/kg/day. This is classified as ACCEPTABLE and satisfies the requirement for a series 82-1 subchronic feeding study in rats.

870.3100 90-Day Oral Toxicity – Mouse

870.3150 90-Day Oral Toxicity – Dog

In a four-week pilot study (MRID 40815004), groups of 4/sex beagle dogs received diets containing diazinon (MG-8) at dose levels of 0, 0.5, 2, 20 or 500 ppm . These dose levels corresponded to 0.02/0.023, 0.073/0.082, 0.80/0.75 or 14.68/15.99 mg/kg/day for males/females. Plasma cholinesterase was inhibited at 0.5 ppm in females at approximately 29%, ($p < 0.01$) and in males at approximately 8% (not significant).

Only at 500 ppm was red blood cell (26-39% in both males and females) and brain (44% in males, 50% in females) acetyl cholinesterase inhibited (all $p < 0.01$). Systemic toxicity was evident at 500 ppm only and included emesis and decreased body weight and feed consumption. For systemic toxicity, the NOAEL is 0.8 mg/kg/day and the LOAEL is 14.68 mg/kg/day based on decreases in body weight. For cholinesterase inhibition, the LOAEL is less than 0.023 mg/kg/day based on plasma cholinesterase inhibition; a NOAEL was not established.

In a 90-day study in dogs (MRID 40815004), groups of 4/sex beagles received diets containing diazinon (MG-8) at dose levels of 0, 0.1, 0.5, 150 or 300 ppm for 13 weeks. These doses correspond to 0.0034/0.0037, 0.020/0.021, 5.9/5.6 or 10.9/11.6 mg/kg/day for males/females. Plasma cholinesterase was inhibited in females at 0.5 ppm at approximately 16% (not significant) and in males at approximately 30% ($p < 0.05$). At 150 ppm, plasma cholinesterase was inhibited about 80% in both males and females. At 150 ppm, red blood cell (~25% in males and ~31% in females, $p < 0.01$) and brain acetyl cholinesterase (31% in males and 30% in females) were inhibited. At 300 ppm, brain AChE was inhibited ~42% in males and ~45% in females.

For systemic toxicity, the NOAEL is 0.021 mg/kg/day and the LOAEL is 5.6 mg/kg/day based on deceased body weight. Systemic effects were noted at 150 ppm and included decreased body weight gain in females (34%, not significant), total protein (~1.4%) and calcium (~5%). At 300 ppm, both male and female body weight gain was decreased (33% males and 45% females), and decreased food consumption and total protein and calcium deceases were increased. For cholinesterase inhibition, the NOAEL is 0.0037 mg/kg/day and the LOAEL is 0.020 mg/kg/day based on plasma cholinesterase inhibition in males.

870.3200 21/28-Day Dermal Toxicity – Rabbit

In a 21-day dermal toxicity study in rabbits (MRID 40660807), four groups of New Zealand strain rabbits (5/sex/dose) received repeated dermal applications of diazinon (97.1% suspended

in 50% polyethylene glycol) at 0, 1, 5 and 100 mg/kg/day, 6 hours/day, 5 days/week over a 21-day period. The high dose of 100 mg/kg/day was reduced to 50 mg/kg/day due to excessive toxicity which manifested as death in 4 of 5 males; these animals exhibited tremors and other signs of cholinergic reactions on days three to six prior to death. The high dose was then reduced to 50 mg/kg/day. Hematology and clinical chemistry were assessed at termination. Serum cholinesterase and RBC and brain acetylcholinesterase was assessed by diagnostic kit (Berringer Mannheim Diagnostics). There were some indications of increased weight gain and food consumption in the rabbits dosed all doses of diazinon but there was no dose response and it considered that the data were too few animals on the study to make a more definite evaluation.

The LOAEL for systemic toxicity is 100 mg/kg/day based on deaths related to cholinergic inhibition symptoms. The NOAEL is 50 mg/kg/day. Serum ChE in females demonstrated 32% ($p < 0.05$), 35% ($p< 0.01$) and 62% ($p < 0.01$) inhibition for the 1, 5 and 50 mg/kg/day dose groups respectively relative to the control group based on group means after three weeks. When compared to the pre-dosing baseline, this progression was 16%, 18% and 57% ($p < 0.01$). Thus, there was no dose response between the 1 and 5 mg/kg/day dose groups. Statistical evaluation by HED staff using pair-wise analysis indicated that only the mid and high dose groups were statistically significant although a trend was evident for all groups. For males, statistically significant inhibition of plasma ChE was evident at 50 mg/kg/day only (64% $p < 0.05$) although there was 23% apparent inhibition at 5 mg/kg/day. RBC AChE was statistically significantly decreased at 50 mg/kg/day (39% for males and 32% for females, both $p < 0.01$). Brain AChE in females was decreased at 5 mg/kg/day (18%; $p < 0.05$) and 50 mg/kg/day (43%; $p < 0.05$). In males there was only one surviving rabbit and brain AChE was decreased 28%. The LOAEL for inhibition of serum ChE and brain AChE is 5 mg/kg/day based on data in females. The NOAEL is 1 mg/kg/day. The LOAEL for inhibition of RBC AChE is 50 mg/kg/day. The NOAEL is 5 mg/kg/day.

870.3250 90-Day Dermal Toxicity – Rat

In a 90-day dermal toxicity study (2011, MRID 48497201), Diazinon (87.4% a.i., lot #090723) was applied to the shaved skin of 10 Sprague-Dawley (Crl: CD (SD)) rats/sex/dose at dose levels of 0, 0.3, 1, 3 or 25 (males-high dose)/10 (females-high dose) mg/kg bw/day, 6 hours/day for 7 days/week during a 90-day period. Additional groups of 5 rats/sex were incorporated into the study for a 4-week recovery period at all dose levels.

Systemic Effects: There were no biologically adverse clinical signs observed with dosage administration up to and including 25 mg/kg/day in males and 10 mg/kg/day in females.

Plasma cholinesterase (ChE): The variability over time for plasma ChE was considered within acceptable limits. Starting at week 1, plasma ChE was decreased up to a maximum of 33% (week 7) in males in the 25 mg/kg/day group. In females, inhibition was up to 42% (week 11, but was as low as 4% at week 10), 59% (week 7, but as low as 20% at week 10), and 82% (week 11 and as low as 58% week 8) in the 1, 3, and 10 mg/kg/day groups, respectively. There was no distinct pattern of increased inhibition over time. An appearance of recovery occurred in males given 25 mg/kg/day and in females given 1, 3 or 10 mg/kg/day.

***Erythrocyte AChE*:** The variability over time and variance affected the interpretation of the data. In males, there was no consistent pattern of lower activity in the 25 mg/kg/day dose group to support definite inhibition. Although at week 1 there was an apparent 13% decrease, the only other time during dosing that statistical significance was attained in males was at week 13. However, although the differences suggested a 38% decrease in activity, the control for this week was unusually high. In females, consistent inhibition of RBC AChE was attained for the 10 mg/kg/day dose group only where the deceases in activity reached to up to 44% (a time when the control was unusually high), more typically the decreases were 20 and 30 percent below the respective control group. The 3 mg/kg/day dose group was considered too variable to conclude there was definite inhibition.

Brain acetylcholinesterase (AChE): assessed at week 13 and after the recovery period only. It was statistically significantly decreased 10% in males in the 25 mg/kg/day group. In females in the 3 and 10 mg/kg/day groups the statistically significant decrease was 6 and 11%, respectively. These changes returned to control levels at the end of the recovery period.

Plasma ChE: In females, the LOAEL for inhibition is 1 mg/kg bw/day and the NOAEL is 0.3 mg/kg/day. *In males,* the LOAEL for inhibition is 25 mg/kg/day and the NOAEL is 3 mg/kg/day.

Erythrocyte AChE: In females, the LOAEL for inhibition is **10 mg/kg bw/day** and the **NOAEL** is **3 mg/kg/day.** A LOAEL in males was not established.

Brain AChE: In females, the LOAEL for inhibition is 3 mg/kg bw/day and the NOAEL is 1 mg/kg/day. *In males,* the LOAEL is 25 mg/kg bw/day and the NOAEL is 3 mg/kg bw/day.

Systemic Toxicity: The LOAEL is >10 mg/kg bw/day in females (HDT) and >25 mg/kg bw/day in males (HDT). No systemic effects were noted at the highest dose in either sex.

Classification. This 90-day dermal toxicity study in the rat is **Acceptable/Non-Guideline** but still satisfies the guideline requirement for a 90-day dermal toxicity study (OPPTS 870. 3250; OECD 411) in rats. The non-guideline status is related to the variability in the ChE assessments especially for the RBC enzyme. No additional dermal toxicity testing is required at this time.

870.3465 90-Day Inhalation – Rat

Groups of Sprague-Dawley rats (15/sex/concentration) were exposed to concentrations of diazinon (MG-8, 87% purity) at 0, 0.1, 1, 10 and 100 µg/L for 6 hours/day, 7 days/week for 21-days. No systemic toxicity was seen at any dose level. For systemic toxicity, the NOAEL is greater than 100 ug/L; a LOAEL was not established. Exposure to diazinon resulted in the inhibition of cholinesterase activity at all concentrations. Exposure to diazinon resulted in plasma, red blood cell (RBC) and/or brain cholinesterase inhibition (AChEI) at all concentration tested. There was a clear dose-depended decreases in ChEI for all three compartments in both sexes. At 0.1 µg/L: plasma ChEI was statistically significant ($p < 0.05$) in males (30%) and females (56%); RBC ChEI was statistically significant ($p < 0.05$) only in males (18%) but not in females (4%); and brain ChEI was not statistically significant in males (4%) or females (6%). At

1 µg/L: plasma ChEI was statistically significant ($p < 0.05$) in males (50%) and females (71%); RBC AChEI was statistically significant ($p < 0.05$) in males (53%) and females (45%); and brain AChEI was statistically significant ($p < 0.05$) in males (13%) or females (15%).

At 10 µg/L plasma ChEI was statistically significant ($p < 0.05$) in males (60%) and females (76%); RBC AChEI was statistically significant ($p < 0.05$) in males (75%) and females (75%); and brain AChEI was statistically significant ($p < 0.05$) in males (37%) and females (44%). At 100 µg/L: plasma ChEI was statistically significant ($p < 0.05$) in males (80%) and females (88%); RBC AChEI was statistically significant ($p < 0.05$) in males (91%) and females (93%); and brain AChEI was statistically significant ($p < 0.05$) in males (62%) or females (80%). For plasma ChEI, a NOAEL is not established for males or females. For RBC AChEI, the NOAEL is 0.1 µg/L in females; a NOAEL is not established for males. For brain AChEI, the NOAEL is 0.1 µg/L for both sexes. For plasma ChEI, the LOAEL is 0.1 µg/L in both sexes. For RBC AChEI, the LOAEL is 0.1 µg/L in males and 1.0 µg/L in females. For brain AChEI, the LOAEL is 1.0 µg/L in both sexes.

A.4.2 Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study – Rat

In a prenatal developmental toxicity study (MRID 00153017), four groups of 27 assumed pregnant rats (Charles River Crl. COBSTM CDTM (SD)(BR)) were dosed as control, 10, 20 or 100 mg/kg/day on days 6 through 15 of gestation. Diazinon (purity not specified) was suspended in 0.2% carboxymethyl cellulose and the rats were dosed by gavage at a rate of 10 mL/kg/day. The rats were sacrificed on day 20 of gestation. At 100 mg/kg/day maternal body weight gain was decreased particularly during the 6-10 day interval (-11±2 gms vs +14±2 gms for the control). After that interval the rats showed recovery but net gain was 25% less for the high dose group at sacrifice. For maternal toxicity, the NOAEL is 20 mg/kg/day and the LOAEL is 100 mg/kg/day based on decreases in body weight gain. The mean fetal weight in the 100 mg/kg/day dose group was increased (~6%) and the mean number of live fetuses in this groups was slightly reduced. There were also noted slight increases in pre and post-implantation loss. An increase in rudimentary T-14 ribs that was within historical control range was also noted. For developmental toxicity the NOAEL is 100 mg/kg/day (HDT); a LOAEL was not established.

870.3700b Prenatal Developmental Toxicity Study – Rabbit

In a developmental toxicity study (MRID 00079017), diazinon (89.2% purity suspended in 0.2% carboxymethyl cellulose) was administered by gavage (1 mL/kg) to four groups of assumed pregnant New Zealand White Rabbits at dose levels of 0 (vehicle control), 7, 25 or 100 mg/kg/day on days 6 to 18 of gestation. At 100 mg/kg/day there were 9 deaths in the group of 22 does (40.9%). Clinical symptoms including tremors and convulsions and body weight gain decreases as well as gastro-intestinal hemorrhages and erosions were noted. The LOAEL for maternal toxicity is 100 mg/kg/day based on deaths. For maternal toxicity, the NOAEL is 25 mg/kg/day and the LOAEL is 100 mg/kg/day based on mortality in dams. No compound related

effects on the fetuses were evident. For developmental toxicity the NOAEL is greater than 100 mg/kg/day; a LOAEL was not established.

A.4.3 Reproductive Toxicity

870.3800 Reproduction and Fertility Effects – Rat

In a multi-generation reproduction study (MRID 41158101), four groups of 30/sex Sprague-Dawley strain rats were dosed as control, 10, 100 or 500 ppm of diazinon (equivalent to 0, 0.67, 6.69 or 35.15 mg/kg/day in male, and 0, 0.77, 7.63 or 41.43 mg/kg/day in females) for 10 weeks and mated (1:1) to produce F1 litter pups. The F1 litters were culled and mated to produce an F2 generation. In the parental groups, at 100 ppm there was deceased weight gain (5-6% persistent for males in the second parental group and transitory for females.). At 500 ppm there were tremors in females; decreased male and female mating and fertility indices (second parental group) and increased gestation length. Dystocia and death were slightly increased but not definitely associated with treatment.

For parental/systemic toxicity, the NOAEL is 0.67 mg/kg/day and the LOAEL is 6.69 mg/kg/day based on decreased parental weight gain. In the pups, at 100 ppm there was mortality and decreased weight gain during lactation. At 500 ppm there were decreases litter size and viable pups. For offspring toxicity, the NOAEL is 0.67 mg/kg/day and the LOAEL is 6.69 mg/kg/day based on pup mortality and decreased weight gain.

A.4.4 Chronic Toxicity

870.4100a (870.4300) Chronic Toxicity – Rat

Sprague-Dawley strain rats (30/sex/dose) received diets containing diazinon (MG-8; 87.7% purity) at dose levels of with 0.0 (two groups), 0.1, 1.5, 125 or 250 ppm diazinon) for 98 weeks (MRID 41942002). These dose levels correspond to 0.004/0.005, 0.06/0.07, 5/6 or 10/12 mg/kg/day for males/females. The control groups (both sets) and the 250 ppm dose group had satellite groups of 10/sex that were reserved for a 4 week recovery period following dosing for 52 weeks. No systemic toxicity was evident. Plasma cholinesterase was inhibited at 1.5 ppm in females (58%, $p < 0.01$) and in males (51%, $p < 0.05$ at termination only). It was noted that at 0.1 ppm at some assay intervals, females were inhibited up to 26% and males up to 36% but statistical significance was not attained. At 125 ppm, red blood cell cholinesterase was inhibited in males (28%, $p < 0.01$) and in females (26%, $p < 0.01$). Brain acetyl cholinesterase was inhibited at 125 ppm for males (24%, $p < 0.01$) and females (29%, $p < 0.01$). For systemic toxicity, the NOAEL is greater than 12 mg/kg/day; a LOAEL was not established. For cholinesterase inhibition, the NOAEL is 0.005 mg/kg/day and the LOAEL is 0.06 mg/kg/day based on of plasma cholinesterase inhibition.

870.4100b Chronic Toxicity – Dog

Groups of beagle dogs (4/sex/dose) dogs were fed diets containing diazinon (MG-8) at dose levels of 0, 0.1, 0.5, 150 or 300/225 ppm for 52 weeks (MRID 41942001). The high dose group

was initiated at 300 ppm but was reduced after 14 weeks to 225 ppm. These dose levels corresponded to 0.0032/0.0037, 0.015/0.020, 4.7/4.5 or 7.7/9.1 mg/kg/day. At 0.5 ppm, plasma cholinesterase was inhibited in females 18-40% ($p < 0.01$). At 150 ppm, red blood cell cholinesterase was inhibited in males (25-34%, $p < 0.01$) and in females (26-33%, $p < 0.01$). Plasma cholinesterase was inhibited at 0.1 ppm (9-28%, $p < 0.05$) in females and at 0.5 ppm 5-25% ($p < 0.05$) in males. Brain acetyl cholinesterase was inhibited at 150 ppm in females (26%, $p < 0.05$) and males (15%, not significant). At 225/300 ppm, male brain inhibition reached 25% but was not significant while female brain inhibition reached 35% ($p < 0.05$). Systemic toxicity was evident at 150 ppm based on decreased body weight gain (up to 64%) and food consumption (up to 27%) particularly in males and increased serum amylase (24-59%). For systemic toxicity the NOAEL is 0.02 mg/kg/day and the LOAEL is 4.5 mg/kg/day based on decreases in body weight gain. For cholinesterase inhibition, the NOAEL is 0.0037 mg/kg/day and the LOAEL is 0.02 mg/kg/day based on plasma cholinesterase inhibition in females.

A.4.5 Carcinogenicity

870.4200a Carcinogenicity Study – Rat

In a carcinogenicity toxicity study (MRID 00073372), diazinon (98% purity) was administered to groups of Fischer 344 (50/sex) rats at either 400 or 800 ppm (estimated to be 20 and 40 mg/kg/day) for 103 weeks. The control group consisted of 25/sex untreated rats. No systemic effects were reported. The study itself did not provide a basis for concluding that adequate doses were assessed. The dose levels tested are well established from other studies to be moderately strong inhibitors of plasma ChE, RBC AChE and brain AChE. No evidence of compound related tumors was apparent in this study. For systemic toxicity, the NOAEL was 40 mg/kg/day; a LOAEL was not established. There was no evidence of carcinogenicity. The doses tested were judged to be adequate to assess the carcinogenic potential of diazinon based on the known property of diazinon to be a moderate inhibitor of ChE/AChE in several other studies at the dose levels tested.

870.4200b Carcinogenicity (Feeding) – Mouse

In a carcinogenicity toxicity study (MRID 00073372), diazinon (98% purity) was administered to 50/sex B63CF1 strain mice in their diets at dose levels of 100 or 200 ppm (estimated to be 14 and 29 mg/kg/day) for 103 weeks. The control group consisted of 25/sex untreated mice. No data on systemic effects were seen. There was no evidence of carcinogenicity. The doses tested were judged to be adequate to assess the carcinogenic potential of diazinon.

A.4.6 Mutagenicity

Gene Mutation

Salmonella typhimurium/ Escherichia coli. MRID 41557404	Independently performed tests were negative in *S. typhimurium* strains TA1535, TA1537, TA98 and TA 100 and *E. Coli* strains WP2 uvrA- up to the highest dose tested (5000 µg/plate ± S9). The test was negative up to the cytotoxic levels (120 µg/mL -S9 and 60 µg/mL +S9)
Mouse lymphoma L5178Y TK± for- ward gene mutation assay. MRIDs 40660802 and 41119701	This test was negative up to cytotoxic levels (120 µg/mL -S9 and 60 µg/mL +S9)
Chromosome Aberration	
Mouse micronucleus assay. MRIDs 40660805 and 41603201	Negative in male and female CD-1 mice up to lethal doses administered by gavage (60 or 120 mg/kg). No evidence of cytotoxic effect on the target cells.
Other Mutagenic Mechanisms	
In vitro sister chromatid ex-change (SCE) in human lymphocytes. MRID 41577301	Study was weakly positive showing reproducible but not dose-related significant increases in SCE frequency over an S9-activated concentrations range of 6.68-66.8 µg/mL. Higher levels (200 µg/mL +S9 or 66.8 µg/mL -S9) were cytotoxic.
In vivo SCE male ICR mice MRID 41687701	The test was negative at oral doses of 10-100 mg/kg. Overt toxicity and bone marrow cytotoxicity were apparent in the treated males at the highest dose tested.
In vivo SCE in female CD-1 strain mice. MRID 43060601	The test was negative in female mice at oral doses of 150-175 mg/kg. Overt toxicity and bone marrow cytotoxicity were apparent in the treated females at concentrations ≥ 150 mg/kg.
Primary rat hepatocyte un-scheduled DNA synthesis. MRID 41557405	Independently performed tests were negative up the highest dose tested (120 µg/mL). Higher levels (≥ 163.1 µg/mL) were insoluble.

A.4.7 Neurotoxicity

870.6100 Delayed Neurotoxicity Study – Hen

870.6200 Acute Neurotoxicity Screening Battery

In an acute neurotoxicity screening study (MRIDs 43132201 and 43132204), groups of 15/sex rats (Sprague-Dawley) were dosed as control 2.5, 150, 300 or 600 mg/kg of diazinon (D-Z-N technical 88% purity) in corn oil by gavage. 10/sex/group were assigned to the main phase of the study to assess for clinical signs, FOB and motor activity; the other five were assessed for ChE/AChE activity. Plasma ChE was inhibited at all dose levels (27% for males and 47% for

females in the 2.5 mg/kg dose group) and RBC AChE was inhibited at 150 mg/kg (83% for males and 76% for females) at the time of peak effect (about 9 hours post-dosing). ChE was equivalent to the controls at day 15 but RBC AChE still remained inhibited for both males and females especially at the higher dose levels. Brain AChE was unaffected when assessed at day 15. The LOAEL for RBC AChE inhibition is 150 mg/kg. The NOAEL for RBC AChE inhibition is 2.5 mg/kg. The LOAEL for plasma ChE inhibition is < 2.5 mg/kg. Based on the FOB assessments, effects at 150 mg/kg included abnormal gait (3/10 males, 7/10 females), ataxic gait (3/10 females), decreased body temperature (-2.1%, females), decreased rearing counts (-33% females), stereotypy (3/10 females) and fecal consistency and stained fur (3/10 males).

Numerous other FOB parameters were affected at 300 mg/kg and above, of these tremors (6/10 females and 5/10 males at 300 mg/kg) were noted and dehydration (6/10 females) were noted. Refer to DER for additional parameters affected. Motor activity was decreased for males (27%, not significant) and females (46%, $p < 0.01$) at 150 mg/kg and above. Body weight gain in males was decreased in the 300 (25%) and 600 (29%) mg/kg dose groups. Deaths (2 males and 1 female) resulted at 600 mg/kg. No histopathological lesions attributed to treatment were indicated. The LOAEL for neurotoxicity is 150 mg/kg based mainly on ataxic gait and supported by other effects believed to be related to ChE/ACHE inhibition. The NOAEL for neurotoxicity is 2.5 mg/kg.

870.6200 Subchronic Neurotoxicity Screening Battery

In a subchronic neurotoxicity study (MRID 43549302) 5 groups of 15/sex Sprague-Dawley Crl CDR BR strain rats were dosed as controls, 0.3, 30, 300 or 3000 ppm corresponding to approximately 0.018, 1.8, 18 and 180 mg/kg/day of D*Z*N diazinon MG87% for 90 days with periodic assessments for clinical signs and FOB, motor activity and blood ChE/AChE. Regional brain AChE activity and neurohistopathology were assessed at termination. Principal clinical signs included (muscle fasciculation, 8/15 females; hyper-responsiveness and tremors, decrease in grip strength: 15-20% in males and 14-39% in females); body weight and gain and food consumption decrease in both sexes were noted at 3000 ppm only. The LOAEL for systemic and neurotoxicity effects is 3000 ppm (180 mg/kg/day) based on weight gain decrease and signs of nervous system perturbation. NOAEL is 300 ppm (18 mg/kg/day). At 30 ppm, plasma ChE (79%-86% in females, 37%-45% in males) and RBC AChE (53-60% in females and 37%-75% in males) and brain AChE cerebral cortex/hippocampus only (25% in females) were inhibited. Other regional brain AChE sources were inhibited at 300 ppm (55%-75% in females) but only at 3000 ppm in males 62% - 73%). Conclusions regarding inhibition of brain AChE are deferred to an accompanying study (MRID No. 43543901) which was especially designed to assess regional brain AChE inhibition. The LOAEL for plasma ChE and RBC AChE inhibition is 30 ppm and the NOAEL is 0.3 ppm.

870.6300 Developmental Neurotoxicity Study

In a developmental neurotoxicity study (MRID 46195601), Diazinon technical (92.9% a.i., batch # 9896144) was administered to 27 female Crl:CD® (SD)BR IGS rats/dose in the diet at concentrations of 0, 0.30, 30 or 300 ppm from gestation day (GD) 6 through postnatal (lactation) day (PND) 21. The average daily test article intake was 0, 0.026, 2.36, or 24.2 mg/kg/day during

gestation and 0.039, 4.06, or 39 mg/kg/day from GD 6 through PND 21. Dietary concentrations were based on a range-finding developmental neurotoxicity study in the rat (MRID 45842601). A Functional Operational Battery (FOB) was performed on 10 dams/dose on GDs 13 and 20, and on PNDs 7, 14, and 20. On PND day 4, litters were culled to yield five males and five females (as closely as possible). Offspring representing at least 20 litters/dose were allocated for detailed clinical observations (FOB), assessment of motor activity, assessment of auditory startle response habituation, assessment of auditory startle pre-pulse inhibition, assessment of learning and memory, and neuropathology at study termination (day 60 of age). On PND day 21, the whole brain was collected from 10 pups/sex/dietary level for micropathologic examination and morphometric analysis. Pup sexual maturation was assessed by age at vaginal opening for females and at completion of balano-preputial separation for males. Plasma, RBC, and brain cholinesterase activities were measured in dams on PND 21, and in selected pups on PNDs 4 and 21.

In dams, no treatment-related effects on mortality, clinical signs, body weight, FOB parameters, or necropsy findings were noted. Piloerection in a few high-dose animals (4/20) on one day (PND 20) is not clear evidence of maternal toxicity. There was a slight decrease in body weight gain (non-statistical - 38%) and food consumption (10%) in the high dose dams during lactation. This is supported by the occurrence of cholinesterase inhibition in all three compartments at the mid dose, and to a greater extent the high dose (discussed below).

In mid- and high-dose dams, cholinesterase activity was significantly inhibited in all three compartments: enzyme activity was inhibited by 67 and 92.6%, respectively, in plasma, by 87.3 and 100%, respectively, in RBC, and by 24.8 and 86.8%, respectively, in brain. No inhibition was measured in low-dose dams.

For maternal systemic toxicity, the NOAEL is 30 ppm (2.36 mg/kg/day), the highest dose tested. A LOAEL was not established.

For maternal cholinesterase inhibition, the NOAEL is 0.3 ppm (0.026 mg/kg/day). The LOAEL is 30 ppm (2.36 mg/kg/day) based decreases in on plasma, RBC and brain cholinesterase activities.

Treatment had no adverse effects on survival, clinical sign, FOB, auditory startle response, brain weights, brain morphology or neuropathology.

No treatment-related effects were noted on body weight or body weight gain for pups in the low- or mid-dose groups. At the high dose, absolute body weights of male and female pups was significantly less ($p \leq 0.05$ or 0.01) than control pups beginning on PND 7 for males and PND 4 for females. Correspondingly, male and female pups from the high-dose group had significantly reduced body weight gain compared with the controls at all intervals throughout lactation. Post-weaning, offspring from the high-dose group had significantly lower body weight compared with the controls through PND 60 for males and PND 42 for females. Weight gain by the high-dose males was significantly less than that of the controls for the first two weeks, but was similar thereafter. Weight gain by the high-dose females was not affected during the post-weaning interval.

Males and females from the high-dose group had significant delays ($p \leq 0.01$) in preputial separation (1.9 days after control) or vaginal opening (1.3 days after control), respectively, compared with the controls. Mean body weight at attainment was similar between the treated and control groups for males and females. In the assessment of motor activity, there was a possible treatment related effect in the high dose males on PND 17, however, it was difficult to interpret the biological significance of this since it only occurred on one day and there was large variability. It was also noted that activity for PND 21 was highly variable across intervals for both males and females. Overall, it was determined that the motor activity assessment was inadequate and difficult to interpret because of too much variability in the data.

In assessment of learning and memory, males from the high-dose group had significantly longer swimming time and a greater number of errors compared to the controls on the first and second day of testing at both PNDs 24 and 60.

In 4-day old male and female pups from high-dose litters, cholinesterase activity was significantly inhibited in plasma by 50.1 and 48.4%, respectively, in RBC by 41.3 and 37.8%, respectively, and in brain by 16.7 and 13.4%, respectively. On PND 21 dose-related inhibition of cholinesterase activity was observed in male and female pups from the mid- and high-dose litters. Plasma enzyme activity was inhibited in the mid- and high-dose offspring by 34.4 and 68.2%, respectively, in males and by 18.6 and 51.2%, respectively, in females. RBC enzyme activity was inhibited in mid- and high-dose males by 23.5 and 58.3%, respectively, and in high-dose females by 53.8%. Males and females from the high-dose group had 44.2 and 28.6% inhibition, respectively, of brain enzyme activity.

For offspring systemic toxicity, the NOAEL is 30 ppm (2.36 mg/kg/day). The LOAEL is 300 ppm (24.2 mg/kg/day) based reduced body weight and body weight gain and delayed sexual maturation in males and females.

For offspring cholinesterase inhibition NOAEL is 0.30 ppm (0.026 mg/kg/day). The LOAEL is 30 ppm (2.36 mg/kg/day) based on plasma, and RBC cholinesterase activities both sexes.

This study is classified **Acceptable/Non-Guideline** and may be used for regulatory purposes. It does not, however, satisfy the guideline requirement for a developmental neurotoxicity study in rats (OPPTS 870.6300, §83-6); OECD 426 (draft) due to the inadequacies in the assessment of motor activity in the offspring and the pending review of the positive control data.

A.4.8 Metabolism

870.7485 Metabolism – Rat

In this study (MRID 41108901) a series of experiments were run with ^{14}C labeled diazinon in Sprague-Dawley strain rats. After 24 hours most of the ^{14}C was recovered in the urine (58.2% & and up to 93.3% %) and smaller amounts (<2.5%) in the feces. After 7 days recovery was 96.7% to 100.25% and < 1% of the label remained in the tissues. The highest level was in the blood.

Three major metabolites were identified in the urine to indicate that diazinon is metabolized to liberate the pyrimidinyl group that is oxidized and excreted. Only trace amounts of parent diazinon were present in the urine or feces. Refer to DER for chemical identification of the metabolites.

870.7600 Dermal Absorption – Rat (Not submitted; special study in human performed, see below)

A.4.9 Immunotoxicity

870.7800 Immunotoxicity

In an immunotoxicity study (MRID 48694201), Diazinon (95.9% a.i., lot #00896074) was administered to female CD-1 mice (10 /dose) in diet at dose levels of 0 (vehicle control), 32, 160, or 800 ppm (equivalent to 0, 6, 32, or 150 mg/kg/day, respectively) for 28 days. On study Day 9, the 800 ppm high dose group was discontinued and these mice were removed from the study due to large decrease in, body weights and water consumption. The 0, 32 and 160 ppm groups were continued as directed by protocol through Day 29. An additional 10 mice were assigned to the cyclophosphamide immunomodulatory positive control group (Group 5) and received a cyclophosphamide 25 mg/kg/day via intraperitoneal injection on Days 24-28. The second arm of the study was conducted with a reduced diazinon high dose and began dosing approximately 3 weeks after the discontinuation of the 800 ppm dose group in dosing arm 1. Dosing arm 2 was comprised of 3 treatment groups (Groups 6-8), each group containing 10 mice per treatment group. Concentrations of 0 (vehicle control) and 400 ppm diazinon were administered in the diet to 10 mice per dose group for 28 days. An additional 10 mice were assigned to the cyclophosphamide immunomodulatory positive control group and received cyclophosphamide 25 mg/kg/day via intraperitoneal injection on Days 24-28. All animals were immunized with single intravenous dose of 0.2 mL of $1x10^8$ sheep red blood cells (SRBC) on Day 24; and euthanized on Day 29 (five days after the immunization). T-cell dependent antibody response (TDAR) to SRBC was evaluated using the ELISA test.

One 800 ppm diazinon mouse was shaking and had hunched posture on Day 8. Also on Day 8, all of the 800 ppm animals had a large reduction in body weights compared to the previous week's weights. These observations were considered related to diazinon administration and as a consequence, all of the 800 ppm diazinon animals were removed from the study on Day 9. There were no test substance-related, clinical signs, and food and water consumption for any of the other study animals. At 400 ppm, there were treatment-related statistically significant ($p<0.05$) decreased in mean body weight throughout the study period, but no effect on the total body weight gains. There were no treatment-related changes in spleen weights and thymus weights in any treated groups.

The systemic toxicity NOAEL is 160 ppm (equivalent to 32 mg/kg/day). The systemic toxicity LOAEL is 400 ppm (equivalent to 75 mg/kg/day) based on reduced body weights.

There were no significant diazinon-related effects on mean anti-SRBC IgM levels in any of the treated groups while compared to the control. High inter-individual variability was seen in the

treatment and vehicle control groups. Examination of individual animal data did not show any trend or distribution that would demonstrate significant suppression of the anti-SRBC IgM response. The positive control group had 93% reduction in the anti-SRBC IgM response. In addition, there were decreased mean absolute and relative spleen weights (↓23.2 and 22.4%, respectively) and absolute and relative thymus weights (↓31.5 and 32.1%, respectively) when compared to the vehicle control group. This confirmed the ability of the test system to detect immunosuppressive effects and confirmed the validity of the study design.

The Natural Killer (NK) cells activity was not evaluated in this study. The toxicology database for Diazinon does not reveal any evidence of treatment related effects on the immune system. The overall weight of evidence suggests that the chemical does not directly target the immune system. Under HED guidance, a NK cell activity assay is not required at this time.

The immunotoxicity NOAEL for this study is 400 ppm (equivalent to 75 mg/kg/day). The immunotoxicity LOEL was not established (>400 ppm).

This immunotoxicity study is classified **acceptable/guideline** and satisfies the guideline requirement for an immunotoxicity study (OPPTS 870.7800) in mice.

A.4.10 Special/Other Studies

Dermal Absorption – Human

In an *in vivo* percutaneous study (**MRID 44982801**), adult human volunteers (6/ group) were dosed dermally with ^{14}C-Diazinon. The application site was washed with soap and water after 24 hours and tape stripped after 7 days. Total urine was collected for 7 days and analyzed for radiolabel. Five rhesus monkeys were dosed intravenously with ^{14}C-Diazinon and total urine and feces collected for 7 days. Urine and feces were analyzed for radiolabel. Rhesus urinary excretion of radiolabel (56%) was used to correct human urinary excretion of radiolabel as a measure of absorbed dose. Dose distribution was as follows:

Group /Dose	Application Site	Formulation Vehicle	Skin Wash (%)	Tape Strip (%)	Urine (%)	Total Recovery (%)	Absorbed (%) [a]
A/ 2 µg/cm^2	Ventral forearm	Acetone	0.4566	0.0096	1.9983	2.4645	3.5584
B/ 2 µg/cm^2	Abdomen	Acetone	1.4448	0.0060	1.8095	1.9603	3.2313
C/ 1.47 µg/cm^2	Abdomen	Lanolin	0.3543	0.0421	1.2757	1.6721	2.2780

[a] Corrected by i.v. rhesus urinary excretion

In a special study (**MRID 43132203**) designed to establish a NOAEL for ChE/AChE, five groups of 15 Sprague-Dawley rats/sex were dosed as control, 2.5, 150, 300 or 600 mg/kg diazinon MG87% (D*Z*N, 88% purity) by gavage in corn oil and were sacrificed in groups of 5/sex after 3, 9 or 24 hours. These intervals were designated as pre-peak, peak and post-peak for effects. The rats were assessed for clinical signs and for plasma ChE, RBC and brain AChE. Clinical signs were first evident in the 300 mg/kg dose group males at 9 hours and at 600 mg/kg

at 3 hours. Males were more frequently affected than females. Plasma ChE was inhibited at 2.5 mg/kg by 30% for males and 60% for females after 9 hours and to a lesser extent at the other intervals. 66-91% inhibition was noted for all other intervals at higher doses. RBC AChE was inhibited 40% ($p < 0.01$) in females dosed with 2.5 mg/kg and 42 to 82% at the higher doses for all other intervals. Four brain regions (cerebellum, cerebral cortex, striatum and hippocampus) and the spinal cord were also assessed. Definite brain AChE inhibition (31 to 68%) was noted at 150 mg/kg in all four regions and the spinal cord. Thus, the LEL for plasma ChE and RBC AChE is < 2.5 mg/kg for both sexes but the NOEL and LEL for brain AChE are 2.5 and 150 mg/kg. Limited correlation between enzyme inhibition with symptoms was apparent since at 9 hours the symptoms were maximal and inhibition (>77% in brain, >74% in RBC and >77% in plasma at 600 mg/kg) were reported but the enzymes remained inhibited when the symptoms regressed at 24 hours.

Another study (**MRID 44219301**) was conducted in two parts to assess the cholinesterase NOAEL and LOAEL and neurotoxicity responses following acute administration. In Part 1, behavioral effects and potential for inhibition of ChE/AChE of Diazinon MG87% was assessed in Sprague-Dawley Crl:CD BR/VAF/Plus strain rats. Part 1 (behavioral effects), four groups of 5 rats/sex were dosed with 0, 100, 250 or 500 mg/kg of diazinon (undiluted) and additional groups of females were dosed with 25 or 50 mg/kg. The rats were observed for clinical signs for 14 days. At 100 mg/kg, females were noted to have one incident of hypoactivity. At 250 and/or 500 mg/kg, miosis, hypoactivity, fur staining, and/or loss of pain reflex occurred, and at 500 mg/kg there was one death. These findings were corroborated by the ChE/AChE part of the study which also demonstrated miosis at 100 mg/kg in a single male rat. The LOAEL is 250 mg/kg based on miosis and hypoactivity. The NOAEL is 100 mg/kg, but this is considered a threshold dose level. In Part 2 (ChE/AChE effects), Seven groups of males were dosed as control, 0.05, 0.5, 1, 10, 100 or 500 mg/kg, and seven groups of females were dosed as control, 0.05, 0.12, 0.25, 2.5, 25 or 250 mg/kg. Animals were sacrificed ~24 hours later. Observations on their behavior reactions were noted, and the blood and brain were assessed for ChE/AChE. The precision of the ChE/AChE assays was considered fair to poor but not sufficiently poor to preclude an assessment of the potential for diazinon to inhibit ChE/AChE. Plasma ChE was inhibited at 2.5 mg/kg in females (61%) and at 10 mg/kg in males (44%). RBC AChE was inhibited at 25 mg/kg in females (35%) and at 100 mg/kg in males (49%). Brain AChE was inhibited at 25 mg/kg in females (36%, not significant) and at 250 mg/kg (70%) and at 500 mg/kg in males (69%). The LOAEL is 2.5 mg/kg based on 61% plasma ChE inhibition in females. The NOAEL is 0.25 mg/kg.

In a special study with humans (**MRID 00091536**; males only), groups of 3 volunteers were dosed with 0.02 or 0.025 mg/kg/day of diazinon (a.i. from Diazinon 50WP) in corn starch by capsule for 38 or 43 days. A control group of 3 was dosed with corn starch only. The LOAEL was 0.025 mg/kg/day based on plasma cholinesterase inhibition. The NOAEL was 0.02 mg/kg/day. Frequent assessments were made every 2 to 3 days of the blood for plasma cholinesterase and red blood cell acetyl cholinesterase. All three volunteers showed inhibition ranging from 8 to 38% in the 0.025 mg/kg/day dose group. Although two of the three volunteers dosed with 0.02 mg/kg/day showed consistent depression ranging from 9 to 30% of plasma cholinesterase relative to their pretest values, a definite conclusion of significant plasma

cholinesterase inhibition could not be established. Red blood cell acetyl cholinesterase was not inhibited.

On January 14, 1999, the HIARC evaluated the study conducted in humans subjects with diazinon (MRID 00091536) and classified this study as *unacceptable* because an audit carried out in 1980 (Clements report) classified this study as "INVALID" based on the following findings: 1) no physician oversight; 2) no rationale for the 'normalization' factor used in data reporting; 3) no analysis of capsules or record of specific dose administered; and 4) no raw data available.

In a special neurotoxicity study (**MRIDs 46166301 and 46166302**), diazinon (92.9% a.i., batch/lot # 9896144) was administered to groups of Crl:CD® (SD) IGS BR rats by gavage. In the acute study, treatment groups consisted of eight adult rats/sex administered single doses of 0, 0.3, 3.0, 30, or 300 mg/kg bw in Mazola® corn oil. Eight PND 11 pups/sex and eight PND 21 pups/sex (one/sex/litter) received single doses of 0, 0.3, 3.0, 10, or 100 mg/kg by gavage. In the repeat dose study, eight male and eight female adult Crl:CD® (SD) IGS BR rats were administered diazinon at 0, 0.03, 0.3, 10, or 100 mg/kg/day in seven consecutive daily doses. Ten male and 10 female pups received doses of 0, 0.03, 0.3, 3, or 30 mg/kg/day from PND 11 to 17. The primary purpose of this study was to determine the effect of diazinon on blood and brain cholinesterase activity in male and female adult and neonatal/juvenile rats following both acute and repeated exposure.

The test material did not did not increase mortality or affect body weight. Following acute dosing, clinical signs of toxicity included tremors in 4/8 adult females at 30 mg/kg, in all adults at 300 mg/kg, in 2/8 female PND 11 pups at 10 mg/kg, and in 7/8 male and 6/8 male PND 11 pups at 100 mg/kg. A high incidence of tremors was noted for all dose groups of PND 17 pups following repeated dosing. Additional clinical signs following acute dosing included rust-colored fur in adults at doses ≥3 mg/kg or ≥0.3 mg/kg following single or repeated doses, respectively; lethargy in 2/8 adult males at 300 mg/kg and in one male and female PND 11 pup at 100 mg/kg; and ataxia in 2/8 male and 2/8 female PND 11 pups at 100 mg/kg. Increased salivation was seen in adults after repeated dosing with 10 mg/kg/day (1/8 males) or 100 mg/kg/day (2/8 males, 3/8 females). Repeated exposure of PND 17 males to 3 or 30 mg/kg/day resulted in decreased absolute brain weight (5% or 9%, respectively).

Acute or repeated exposure to diazinon resulted in statistically and biologically significant decreases in the cholinesterase activity in plasma, red blood cell (RBC), and brain of young adult animals, and PND 11, PND 17, and PND 21 pups. In adults, effects were noted at 3 mg/kg in both sexes following single dose exposures and at 0.3 mg/kg/day in females after repeated exposures. Following single doses to pups, effects were observed at 3 mg/kg in both sexes of PND 11 pups and in both sexes of PND 21 pups. After repeated exposures, effects were noted in PND 17 pups at 0.3 mg/kg/day in both sexes. Acute doses of 0.3 mg/kg and repeated doses of 0.03 mg/kg caused no significant effects.

For acute exposure:

the adult LOAEL for plasma ChEI is 3 mg/kg (both sexes)

the PND 11 LOAEL for plasma ChEI is 3 mg/kg (both sexes)
the PND 21 LOAEL for plasma ChEI is 3 mg/kg (both sexes);

the adult NOAEL for plasma ChEI is 0.3 mg/kg (both sexes)
the PND 11 NOAEL for plasma ChEI is 0.3 mg/kg (both sexes)
the PND 21 NOAEL for plasma ChEI is 0.3 mg/kg (both sexes);

the adult LOAEL for red blood cell ChEI is 30 mg/kg (males), >300 mg/kg (females)
the PND 11 LOAEL for red blood cell ChEI is 100 mg/kg (males), 10 mg/kg (females)
the PND 21 LOAEL for red blood cell ChEI is 100 mg/kg (both sexes);

the adult NOAEL for red blood cell ChEI is 3 mg/kg (males), ≥300 mg/kg (females)
the PND 11 NOAEL for red blood cell ChEI is 10 mg/kg (males), 3 mg/kg (females)
the PND 21 NOAEL for red blood cell ChEI is 10 mg/kg (both sexes);

the adult LOAEL for brain ChEI is 300 mg/kg (males), 30 mg/kg (females)
the PND 11 LOAEL for brain ChEI is 10 mg/kg (both sexes)
the PND 21 LOAEL for brain ChEI is 10 mg/kg (both sexes);

the adult NOAEL for brain ChEI is 30 mg/kg (for males), 3 mg/kg (females)
the PND 11 NOAEL for brain ChEI is 3 mg/kg (both sexes)
the PND 21 NOAEL for brain ChEI is 3 mg/kg (both sexes).

For acute exposure, the overall LOAEL for cholinesterase inhibition in adults is 3 mg/kg based on plasma; the adult NOAEL is 0.3 mg/kg.

For acute exposure, the overall LOAEL for cholinesterase inhibition in PND 11 and PND 21 pups is 3 mg/kg based on plasma; the pup NOAEL is 0.3 mg/kg.

For repeated exposure:

the adult LOAEL for plasma ChEI is 10 mg/kg/day (males), 0.3 (females)
the PND 17 LOAEL for plasma ChEI is 0.3 mg/kg/day (both sexes);

the adult NOAEL for plasma ChEI is 0.3 mg/kg/day (males), 0.03 (females)
the PND 17 NOAEL for plasma ChEI is 0.03 mg/kg/day (both sexes);

the adult LOAEL for red blood cell ChEI is 10 mg/kg/day (males), 100 mg/kg/day (females)
the PND 17 LOAEL for red blood cell ChEI is 30 mg/kg/day (males), 3 mg/kg/day (females);

the adult NOAEL for red blood cell ChEI is 0.3 mg/kg/day (males), 10 mg/kg/day (females)
the PND 17 NOAEL for red blood cell ChEI is 3 mg/kg/day (males), 0.3 mg/kg/day (females);

the adult LOAEL for brain ChEI is 100 mg/kg/day (males), 10 mg/kg/day (females)
the PND 17 LOAEL for brain ChEI is 3 mg/kg/day (both sexes);

the adult NOAEL for brain ChEI is 10 mg/kg/day (males); 0.3 mg/kg/day (females)
the PND 17 NOAEL for brain is 0.3 mg/kg/day (both sexes).

For repeated exposure, the overall LOAEL for cholinesterase inhibition in adults is 0.3 mg/kg/day based on plasma; the NOAEL is 0.03 mg/kg/day.

For repeated exposure, the overall LOAEL for cholinesterase inhibition in PND 17 pups is 0.3 mg/kg/day based on plasma; the NOAEL is 0.03 mg/kg/day.

Different gavage doses in adult and juvenile rats made sensitivity comparisons difficult. At an acute dose of 3 mg/kg, sensitivity of adults and juveniles as indicated by plasma ChEI was similar. However, when comparing percent inhibition for each compartment at the higher doses, the similar values for juveniles at 10 mg/kg and adults at 30 mg/kg indicates greater susceptibility for juveniles. The same was true for the 300 mg/kg dose in adults and the 100 mg/kg dose in juveniles. For repeat dosing, plasma ChEI was similar for adults and juveniles at 0.3 mg/kg/day. However, at the higher doses, percent inhibition of adults at 10 mg/kg/day was similar to that of juveniles at 3 mg/kg/day; the same relationship was observed at 100 mg/kg/day (adults) and 30 mg/kg/day (juveniles). This indicates that juvenile rats are more susceptible than adults.

This study is classified **acceptable/nonguideline** for the determination of plasma, RBC, and brain cholinesterase activities following treatment with diazinon in adult, neonatal/juvenile, and fetal rats. There was no assessment in dams and GD 20 fetuses, but a developmental neurotoxicity study with cholinesterase evaluation was conducted for diazinon.

The following Executive Summaries are on the oxon.

In a pilot/tolerance study (**MRID 48663501**), Diazoxon (98.7 % a.i., batch # RH 589.14) was administered as a single or repeated (7 day) oral gavage dose to young adult (Phase I) and postnatal day (PND) 11 neonatal/juvenile (Phase II) Crl:CD(SD)IGS rat pups. In both Phases, mortality, clinical signs, detailed physical/behavioral and arena observations, body weight, brain weight and macropathology were assessed. Data were presented for plasma, RBC and brain ChE for the terminal sacrifice only.

Phase I -Young Adult Rats

In Phase I, young adult rats (2/sex/group) received (I) a single oral gavage dose at 0, 0.3, 30, 60 or I 00 mg/kg body weight (Phases I A and B) or (2) repeated oral doses at 0, 3, 30 (two separate groups) or 45 mg/kg for up to seven consecutive days (Phases I C and D).

Single Dose: *Systemic Effects.* All rats in the 60 or 100 mg/kg group were sacrificed between 40 minutes and approximately 2 hours post dosing due to deteriorating clinical condition. Clinical signs included piloerection, under-active behavior, uncoordinated and/or elevated gait, partially closed eyes, and reduced body tone. At these doses, marked inhibition of ChE was observed in plasma (94-95%) and erythrocytes (86%-87%). However, brain ChE

activity was not affected in either dose in females. In males, brain ChE activity was inhibited 7% at the 100 mg/kg dose. Thus, a single dose of 60 mg/kg exceeded the maximum tolerated dose.

ChE Inhibition in the survivors. All rats dosed at 0.3 or 30 mg/kg survived until sacrificed at 9 hr post dosing and tolerated these doses without clinical signs. In the 30 mg/kg group, plasma ChE activity was inhibited by 68% and 82% in males and females, respectively, and inhibition of erythrocytes ChE activity ranged 73-78% among males and females. At 0.3 mg/kg, 21%-31% inhibition in plasma and 12%-29% inhibition in erythrocytes ChE were noted among males and females. Females appeared to be affected to a greater extent than males. Brain ChE activity was not affected at 0.3 or 30 mg/kg.

Repeated Dosing: *Systemic Effects.* All animals tolerated administration of diazoxon with no consistent clinical signs. In one of the 30 mg/kg groups, signs of underactive behavior, reduced body tone, uncoordinated and/or elevated gait, partially closed eyes and piloerection were noted on Day 1 after dosing. However, these signs were not also noted in the other group of animals dosed at 30 mg/kg or at higher doses. No clear relationship between mean body weight and treatment with Diazoxon was observed.

ChE Inhibition in survivors. Administration of 3 mg/kg resulted in 42-43% inhibition of ChE activity in plasma and 56-61% inhibition in erythrocytes in both sexes. At 30 mg/kg/day, effects on ChE were similar in both groups with plasma ChE demonstrating 71-97% inhibition, and erythrocytes demonstrating 81-84% inhibition. At 45 mg/kg, a marked inhibition of ChE was noted in plasma (73-82%) and erythrocytes (83-85%) in both sexes. Brain ChE activity was not affected at 3 mg/kg/day. However, females (2-11%) but not males dosed at 30 mg/kg/day demonstrated slight brain ChE inhibition. Brain ChE was inhibited by 18% and 21% in the 45 mg/kg males and females, respectively.

Phase II -Neonatal/Juvenile Rats

In Phase II, neonatal/juvenile rats (pups, 8/sex for controls and 3/sex/group for the dosing animals) were given (1) a single oral dose at 0, 3, 10, 20 or 30 mg/kg (Phase IIA) or repeated oral doses at 0, 1,3, 6 or 10 mg/kg for seven consecutive days (Phase JIB).

Single Dose: *Systemic Effects.* All pups were sacrificed following a single dose of 20 or 30 mg/kg between I - 1.5 hours post due to deteriorating clinical condition. At 20 mg/kg and above, signs of unsteady gait, cold to touch, tremors, underactive behavior, flattened gait and gasping respiration were observed at 1-hour. Inhibition of ChE in plasma (88-94%), erythrocytes (88- 89%) and brain (83-87%) was noted. At 30 mg/kg, brain ChE activity was severely inhibited by 96-97% in males and females.

At 3 or 10 mg/kg all pups survived to the scheduled sacrifice. At 10 mg/kg, transient tremors were observed in all animals from 1.5-2 hours after dosing and underactive behavior was noted in 5 of the 6 animals. Most of these signs had resolved by the 3-hour observation. No clinical signs were observed at the 3 mg/kg dose.

ChE Inhibition in survivors. Plasma and erythrocyte ChE was inhibited 61-65% respectively, at the 3 mg/kg dose. At 10 mg/kg, plasma ChE was inhibited by 75-76% whereas erythrocytes ChE was inhibited 83% and 78% in males and females, respectively. Brain ChE was 19-20% inhibited at the 10 mg/kg dose among males and females. No inhibition of brain ChE activity observed in the 3 mg/kg.

Repeated Dosing: *Systemic Effects.* No mortality occurred at dose levels of 1, 3, or 6 mg/kg in neonatal/juvenile rats. However, at 10 mg/kg, all pups were sacrificed between 3.5 hours and approximately 6 hours after administration of the third dose. No clinical signs were apparent on Day 1 of treatment. Clinical signs of tremors, underactive behavior, unsteady gait and splayed hindlimbs occurred at low incidence on Day 2 and signs of tremor were noted in all animals at the 1-hour observation on Day 3.

ChE Inhibition. There was 63-82% inhibition of plasma and 52-82% inhibition of erythrocyte ChE at doses of 1, 3 or 6 mg/kg in males and females. At 10 mg/kg plasma (93-96%) and erythrocytes (88-89%) ChE inhibition was noted. Inhibition of brain ChE was not affected in the 1 mg/kg group or 3 mg/kg group females. Brain ChE was inhibited to 8% in males at 3 mg/kg, 11-23% in males and females at 6 mg/kg and 74-75% at 10 mg/kg/day.

Overall Conclusions. Results indicate that at higher doses, rat pups are more sensitive to single and repeated administration of diazoxon compared to young adults. Based on results of this study, the dose levels of 10 mg/kg for pups and 45 mg/kg for young adults are suitable doses for use in subsequent acute time-to-peak effect studies.

Classification: This study is classified as acceptable/non-guideline.

In a single dose time to peak effect study (2011, **MRID 48663502**), groups of postnatal day (PND) 11 neonatal/juvenile Crl:CD(SD)IGS rat pups (15/sex/dose) were given a single oral (gavage; 5mL/kg) dose of Diazoxon (98.7 % a.i., batch # RH 589.14) in com oil at doses of 0 or 10 mg/kg bw. Three males and three females from each group were killed at 45 minutes, 90 minutes, 3 hours, 6 hours or 9 hours after dosing. Mortality, clinical signs, detailed physical/behavioral and arena observations, blood (plasma and erythrocytes) and brain cholinesterase, brain weight and macropathology were performed during the course of the study.

All neonatal/juvenile rats survived to scheduled sacrifice except for one 10 mg/kg bw male that was sacrificed at approximately 80 min after dosing. Clinical signs of toxicity in this pup were gasping respiration, tremors and pallor. Severe inhibition of ChE activity was reported in plasma, erythrocytes and brain samples.

Behavioral assessment. In general, a low incidence of behavioral changes was reported in the arena and all signs observed were graded as slight. Lower activity counts were apparent in the I0 mg/kg group females at I hour and 15 minutes whereas treated males showed only slightly lower activity counts. Signs included soft excessive vocalization (1 male and 1 female), slight head tremor (1 female), slight whole body tremor (1 male) and slight twitch whole

body (1 male). At 2 hours and 45 minutes, activity accounts were decreased in the 10 mg/kg group males and females. Signs of slight whole body tremor and yellow ano-genital staining were observed in one treated male.

ChE Inhibition. At 45 minutes, marked inhibition of ChE activity was observed in plasma (82- 83%) and erythrocytes (69-76%) among treated males and females. Whereas, only slight inhibition of brain ChE activity was noted in treated males (14%) and females (12%). Similar plasma levels of ChE inhibition were noted in treated males (83-88%) and females (83-86%) between 90 min and 6 hrs. There appeared to be a decrease in the level of ChE inhibition in plasma and erythrocytes in both sexes between 6 hr and 9 hr after dosing. In brain, there was a gradual and progressive increase in the level of ChE inhibition between 45 min and 6 hr in treated females (12-35%). Inhibition in treated males over this time period fluctuated between 14-39%. The level of inhibition of brain ChE was reduced to 27% in treated males and to 22% in treated females by 9 hrs after dosing.

It is concluded that there was no clear evidence upon which to establish the time to peak effect of Diazoxon based on the behavior of neonatal/juvenile rats. The results obtained in this study were inconclusive since the incidences of behavioral changes reported in the arena were low, occurred only occasionally in animals. The differences observed during the assessment of activity counts were attributed to natural variation and were considered unrelated to treatment based on the absence of clear signs of toxicity and the large variability previously seen in activity counts. The small group size (3/sex at each assessment time) used in this study did not provide enough power to overcome the variability in the measurements.

Based on the results of ChE assessment, particularly in the brain versus the plasma and erythrocyte ChE activity, the time to peak effect of acute dosing of neonatal/juvenile rats with Diazoxon was 6 hours. This time to peak effect can be used in subsequent single and repeated dose comparative sensitivity studies using 11 Day old neonatal/juvenile Crl:CD(SD)IGS rats.

Classification. This study is classified as acceptable/non-guideline and provides sufficient data to establish the time to peak effect for ChE inhibition but is considered limited in establishing the time to peak effect for behavioral reactions.

In a single dose time to peak effect study (2011, **MRID 48663503**), groups of young adult Crl:CD(SD)IGS rats (15/sex/dose) were given a single oral (gavage; 5mL/kg) dose of diazoxon (98.7% a.i., batch # RH 589.14) in corn oil at doses of 0 or 45 mg/kg bw. Three males and three females from each group were killed at 45 minutes, 90 minutes, 3 hours, 6 hours or 9 hours after dosing. Mortality, clinical signs, detailed physical/behavioral and arena observations, blood (plasma and erythrocytes) and brain cholinesterase, brain weight and macropathology were performed during the course of the study.

Administration of diazoxon at a single dose of 45 mg/kg resulted in no mortality. During the in-the-hand observation assessment, there were no treatment-related effects on behavior. Signs were seen in single animals and limited to piloerection (at 1 hr and 15 min and 2 hr and 45 min) or brown ano-genital staining (at 2 hr and 45 min and 5 hr and 45 min). However, these animals appeared normal at the 8 hr and 45 min observation.

Several behavioral signs were apparent 30 minutes post-dosing during arena observations and included partial reduced arousal, slight occasional whole body tremor, palpebral closure,

hunched and flattened posture, elevated gait, slow/labored breathing and slight tremor. Reduced activity and rearing scores were evident. At 1 hr and 15 min, signs of piloerection, palpebral closure, occasional whole body tremor and hunched posture were still apparent in treated males and/or females. Some signs were still apparent at the subsequent time-point of observations (2 hr and 45 min), however, the incidence and severity of the signs decreased as time went on.

Marked inhibition of ChE was observed in plasma (82-90%) and erythrocytes (82-87%) at 45 minutes after dosing in treated males and females when compared to controls. Levels of ChE inhibition in plasma were 85-90% from 90 min to 6 hrs in treated males, whereas in treated females levels of ChE inhibition were 79-83% at the same time-points. In erythrocytes, levels of ChE inhibition were 91-93% (males) and 64-94% (females) from 90 min to 6 hr. The degree of erythrocytes ChE inhibition was lower at the 9-hours in treated males (84%) and females (87%) compared to the 90 min and 6 hr time-points. Neither brain ChE activity nor brain weight was affected by diazoxon at any time-point.

It was concluded that arena observations demonstrated that the time to peak effects on behavior was 30 minutes post-dosing. On the other hand, the time to peak effects on ChE was 90 minutes post-dosing, based on the results of the ChE activity assessment, particularly the degree of inhibition of ChE observed in the erythrocytes. Consequently, the time to peak effects for young adult rats in this study was determined to be 1 hour post-dosing, in order to capture both behavioral and enzyme inhibition peaks.

Classification: This study is classified as **acceptable/non-guideline.**

In a comparative sensitivity study (**MRID 48663504**), Crl:CD(SD)IGS rats were administered a single dose of diazoxon (98.7% a.i., batch # RH 589.14) in corn oil by gavage. Mortality, clinical signs, detailed physical/behavioral and arena observations were assessed. The optimal post dosing times for assessment were previously determined to be 45 min for adults and six hours for the pups after dosing for blood (plasma and erythrocytes) and brain cholinesterase (ChE), brain weight and macropathology assessments.

Phase I – Young Adult Rats

Young adults (8/sex/dose) were dosed at 0, 0.2, 2, 10, or 45 mg/kg bw.

Systemic effects. At 10 mg/kg treatment-related findings in one male included hunched posture, flattened gait, whole body tremor and piloerection. One female had flattened gait. At 45 mg/kg four males and two females were affected and demonstrated signs including reduced arousal, minor gait abnormalities (elevated or flattened), hunched posture, whole body tremor, piloerection, reduced activity and rearing scores and loose feces.

ChE Inhibition. Plasma ChE was statistically significantly ($p < 0.05$ or 0.01) inhibited in males by 23%, 63%, 87% and 94% and in females by 35%, 60%, 82% and 91% for the 0.2, 2, 10 and 45 mg/kg dose groups, respectively demonstrating a clear dose response. *RBC* ChE was significantly inhibited by 53%, 81% and 92% in males and 38%, 74% and 90% in

females for the 2, 10 and 45 mg/kg dose groups, respectively, also demonstrating a clear dose response. *Brain* ChE was not inhibited.

Phase II – PND 11 Neonatal/Juvenile Rats (Pups)

Postnatal day (PND) 11 rat pups (8/sex/dose) were dosed at 0, 0.2, 2, 5, or 10 mg/kg bw.

Systemic Effects. There was no mortality. No consistent treatment related effects on arena parameters were observed at any dose level at 5 hours and 45 minutes after dosing.

ChE Inhibition. Plasma ChE was statistically inhibited (all $p < 0.01$) by 19%, 56%, 75% and 81% for males and 22%, 62%, 76% and 84% for females for the 0.2, 2, 5 and 10 mg/kg dose groups, respectively. *RBC* ChE was statistically inhibited by 51%, 82% and 85% in males and 50%, 78% and 85% in females for the 2, 5, and 10 mg/kg dose groups, respectively. Unlike the young adults, *brain* ChE was statistically inhibited by 20% and 29% in males and by 9% ($p< 0.05$) and 26% in females for the 5 and 10 mg/kg dose groups, respectively.

Comparison of Young Adults and Pups.

Both young adults and pups have the same LOAELs for inhibition of both plasma (0.2 mg/kg) and RBC (2 mg/kg) ChE and inspection of the dose responses indicates similar inhibition at the common doses. Therefore, the neonatal pups are not more sensitive than young adults to diazoxon inhibition to plasma and RBC ChE when the NOAEL and LOAEL assignment is considered. However, the pups but not adults demonstrated inhibition of brain ChE by diazoxon.

-The LOAEL for plasma ChE is 0.2 mg/kg for both sexes at both ages. The NOAEL was not established.
-The LOAEL for *RBC* ChE is 2 mg/kg for both sexes at both ages. The NOAEL is 0.2 mg/kg.
-The LOAEL for pup *brain* ChE is 5 mg/kg for both sexes. The NOAEL is 2 mg/kg. The LOAEL of adult brain ChE is > 45 mg/kg.

Classification. This study is classified as **acceptable/non-guideline**.

In a comparative sensitivity study (**MRID 48663505**), young adult and PND 11 neonatal/juvenile pups of the Crl:CD(SD)IGS rat strain (8/sex/dose) were given a daily oral (gavage; 5mL/kg) dose of diazoxon (98.7 % a.i., batch # RH 589.14) in com oil. Both age groups were dosed as 0, 0.05, 0.1, 1, or 5 mg/kg bw/day for 7 consecutive days.

Mortality, clinical signs, detailed physical/behavioral and arena observations, blood (plasma and erythrocytes) and brain cholinesterase (ChE), brain weight and macropathology were performed during the course of the study. Pilot studies (MRIDs 48663501 and 48663503) determined the dose levels and time to peak effect (one hour for adults and 6 hours for pups) parameters.

Phase I – Young Adult Rats

Systemic Effects. There was no effect on survival. Body weight was unaffected, and there were no clinical signs of toxicity, observations in the hand or macroscopic abnormalities. In the arena evaluations, although some statistical differences were noted in scores such as for rearing score, it was concluded that they were either incidental or not otherwise a toxicological concern in this study that was designed mainly to determine if the neonatal pups are more sensitive than the adults since, for example, no effects in rearing were noted in the pups.

ChE Inhibition. Plasma ChE was statistically significantly lower by 17%, 30%, 40% and 72% among males for the 0.05, 0.1, 1 and 5 mg/kg/day dose groups and 32%, 63% and 80% for the 0.1, 1 and 5 /g/kg/day dose females, respectively. Thus there is a good dose response and a demonstration that males may be more sensitive than females for plasma ChE inhibition. *RBC* ChE was inhibited to 31% and 74% in males and 37% and 71% in females for the 1 and 5 mg/kg/day groups indicating similar sensitivity for each sex. *Brain* ChE was not inhibited in either sex.

Phase II – PND 11 Neonatal/Juvenile Rats

Systemic Effects. There was no effect on survival. Body weight was unaffected, and there were no clinical signs of toxicity or macroscopic abnormalities. No treatment related effects were observed on arena parameters at 5 hours and 45 minutes after dosing.

ChE Inhibition. Plasma ChE was statistically significantly lowered to 13%, 30, 60% and 83% in males and 14%, 27%, 58% and 86% in females for the 0.05, 0.1, 1 and 5 mg/kg/day dose groups, thus demonstrating similar inhibition with good dose response in both sexes. For *RBC* ChE there was 60% and 80% inhibition in males and 68% and 89% inhibition in females for the 1 and 5 mg/kg/day dose groups, respectively. *Brain* ChE was inhibited to 22% in males and 23% in females in the high dose group.

Overall conclusion. The PND 11 pups are not more sensitive to ChE inhibition by diazoxon than young adult rats based on similar NOAELS and LOAELs. The pups were demonstrated to be susceptible to brain ChE inhibition but the young adults were not.

The degree of plasma ChE inhibition observed at the lowest dose tested (0.05 mg/kg/day) in young adults (↓17%) and PND 11 pups (↓13-14%) was considered to be lower than the limit considered to be biologically relevant.

-The LOAEL for *plasma* ChE and RBC ChE is 0.1mg/kg/day for both sexes and both ages. The NOAEL is 0.05 mg/kg/day.

-The LOAEL for *brain* ChE is 5 mg/kg/day for both sexes of pups. The NOAEL is 1 mg/kg/day. Brain ChE was not inhibited in adults (LOAEL > 5 mg/kg/day).

Classification: This study is classified as acceptable/non-guideline. It is noted that the repeat dosing study was for only seven daily doses.

A.5. Sex and Life Stage Sensitivity

Table A.5.1. Results of BMD Modeling (mg/kg) for Brain and RBC ChE Data on Diazinon, Acute Oral Dosing Studies in Rats.

Test	Age Sex	Brain BMD_{10}	Brain $BMDL_{10}$	RBC BMD_{10}	RBC $BMDL_{10}$
MRID 46166301 Acute CCA	Adult Male	NF		NF	
MRID 46166301 Acute CCA	Adult Female	6.824	6.492	NF	
MRID 46166301 Acute CCA	PND 11 Male	NF		NF	
MRID 46166301 Acute CCA	PND 11 Female	3.194	2.925	3.362	2.963
MRID 43132203 Acute TC (9 hours)	Adult Male	14.702 [a]	12.175	6.932	4.804
MRID 43132203 Acute TC (9 hours)	Adult Female	12.876 [a]	9.218	NF	
MRID 43132204 Acute Neurotoxicity	Adult Male	NE		4.146	1.823
MRID 43132204 Acute Neurotoxicity	Adult Female	NE		5.229	1.754

[a] Value for the brain cortex.
CCA = Comparative Cholinesterase Assay
Acute TC = Time course for ChE inhibition following a single dose
NF = no model fit
NE = Not evaluated with BMD analysis, due to obvious lack of dose response

Table A.5.2. Results of BMD Modeling (mg/kg/day) for Brain and RBC ChE Data on Diazinon, Repeated Oral Dosing Studies in Rats.					
Test (dosing days)	Age Sex	Brain BMD_{10}	Brain $BMDL_{10}$	RBC BMD_{10}	RBC $BMDL_{10}$
MRID 46166302 Repeated Dose CCA (7)	Adult Male	23.639	19.625	2.339	0.284
MRID 46166302 Repeated Dose CCA (7)	Adult Female	3.425	3.118	NF	
MRID 46166302 Repeated Dose CCA (7)	PND 11 Male	NF		3.066	2.942
MRID 46166302 Repeated Dose CCA (7)	PND 11 Female	2.759	1.255	0.524	0.351
MRID 40815003 13-Week Oral Tox (87)	Adult Male	24.668	21.998	3.408	0.210
MRID 40815003 13-Week Oral Tox (87)	Adult Female	2.868	2.572	0.221	0.166
MRID 43543902 Subchronic NT (Week 13)	Adult Male	12.405 [b]	4.644	NF	
MRID 43543902 Subchronic NT (Week 13)	Adult Female	1.306 [b]	1.103	0.183	0.139
MRID 45842601 RF DNT (21)	Adult Female (Dam)	1.242	1.057	NF	
MRID 45842601 RF DNT	Fetus M & F	NE		NE	
MRID 45842602 RF DNT (15)	Adult Female (Dam)	1.648	1.175	0.123	0.123
MRID 45842602 RF DNT	Fetus Male	0.957	0.468	1.687	1.223
MRID 45842602 RF DNT	Fetus Female	11.552	7.996	16.605	1.701
MRID 46195601[a] DNT (16)	Adult Female (Dam)	1.429	1.246	NF	
MRID 46195601[a] DNT	Male PND 4	24.324	16.672	8.751	6.420
MRID 46195601[a] DNT	Female PND 4	NE		NE	

[a] Hill model allowed the best fit.
[b] Value for the brain cortex.
RF = Range finder
DNT = Developmental neurotoxicity test
CCA = comparative cholinesterase assay
NE = Not evaluated with BMD analysis, due to lack of dose response
NF = no model fit

Table A.5.3. Results of BMD Modeling (mg/kg/day) for Brain and RBC ChE Data on Diazinon, Oral Toxicity in Dogs.					
Test (dosing days)	Age Sex	Brain BMD_{10}	Brain $BMDL_{10}$	RBC BMD_{10}	RBC $BMDL_{10}$
MRID 40815004 13-Week Oral Tox (92)	Adult Male	1.425	0.892	NT	
MRID 40815004 13-Week Oral Tox (92)	Adult Female	1.369	1.089	NT	
MRID 40815004 13-Week Oral Tox (86)	Adult Male	NT		NF	
MRID 40815004 13-Week Oral Tox (86)	Adult Female	NT		NE [a]	
MRID 40815004 13-Week Oral Tox (56)	Adult Male	NT		1.416	1.029
MRID 40815004 13-Week Oral Tox (56)	Adult Female	NT		0.992	0.786

[a] No dose response: 3075 mU/mL for control and low dose, 2950 mU/mL for mid-dose, and 2125 mU/mL for the two highest doses (0, 0.1, 0.5, 150 and 300 ppm).
NT = Cholinesterase Inhibition Not tested in the study
NE = Not evaluated with BMD analysis, due to lack of dose response
NF = no model fit

Table A.5.4. Results of BMD Modeling (mg/kg/day) for Brain and RBC ChE Data on Diazinon, Dermal Toxicity in Rats.					
Test (dosing days)	Age Sex	Brain BMD_{10}	Brain $BMDL_{10}$	RBC BMD_{10}	RBC $BMDL_{10}$
MRID 48497201 13-Week Dermal Tox (Week 13)	Adult Male	NF		NF	
MRID 48497201 13-Week Dermal Tox (Week 13)	Adult Female	NF		0.077	0.068
MRID 46903001 4-Week Dermal Tox (Week 4)	Adult Male	NE		218.095 [a]	182.572
MRID 46903001 4-Week Dermal Tox (Week 4)	Adult Female	NE		469.587	388.799
MRID 46903001 4-Week Dermal Tox (Week 2)	Adult Male	NE		221.358 [a]	183.398
MRID 46903001 4-Week Dermal Tox (Week 2)	Adult Female	NE		371.930	345.433

[a] Hill model allowed the best fit.
NE = Not evaluated with BMD analysis, because RBC ChE inhibition is more sensitive than brain ChE inhibition.
NF = no model fit

Table A.5.5. Results of BMD Modeling (mg/L/day) for Brain and RBC ChE Data on Diazinon, Inhalation Toxicity in Rats. [a]					
Test (dosing days)	Age Sex	Brain BMD_{10}	Brain $BMDL_{10}$	RBC BMD_{10}	RBC $BMDL_{10}$
MRID 41557402 21-Day Inhalation Tox (21)	Adult Male	NE		0.00236	0.00183
MRID 41557402 21-Day Inhalation Tox (21)	Adult Female	NF		0.00099	0.00082

[a] Exposure was nose-only for 6 hours each day for 7 consecutive days.
NE = Not evaluated with BMD analysis, due to obvious lack of dose response
NF = no model fit

Table A.5.6. Results of BMD Modeling (mg/kg) for Brain and RBC ChE Data on Diazoxon, Acute Oral Dosing CCA Studies in Rats.					
Test	Age Sex	Brain BMD_{10}	Brain $BMDL_{10}$	RBC BMD_{10}	RBC $BMDL_{10}$
MRID 48663504 Acute CCA	Adult Male	NE [b]		0.234 [a]	0.168
MRID 48663504 Acute CCA	Adult Female	NE [b]		0.371 [a]	0.280
MRID 48663504 Acute CCA	PND 11 Male	NE [c]		NF	
MRID 48663504 Acute CCA	PND 11 Female	NE [c]		0.275	0.237
MRID 48663501 RF Acute CCA	Adult Male	NE [d]		NE [d]	
MRID 48663501 RF Acute CCA	Adult Female	NE [d]		NE [d]	
MRID 48663501 RF Acute CCA	PND 11 Male	7.608	6.592	0.177 [a]	0.115
MRID 48663501 RF Acute CCA	PND 11 Female	7.909	6.929	0.300 [a]	0.188

[a] Hill model allowed the best fit.
[b] No dose response
[c] RBC ChE inhibition is more sensitive than brain ChE inhibition.
[d] n=2
CCA = Comparative Cholinesterase Assay
NF = no model fit well
NE = Not evaluated with benchmark modeling
RF = Range Finding

Table A.5.7. Results of BMD Modeling (mg/kg/day) for Brain and RBC ChE Data on Diazoxon, Repeated Oral Dosing CCA Studies in Rats.					
Test (dosing days)	Age Sex	Brain BMD_{10}	Brain $BMDL_{10}$	RBC BMD_{10}	RBC $BMDL_{10}$
MRID 48663505 Repeated Dose CCA (7)	Adult Male	NDR		0.260	0.196
MRID 48663505 Repeated Dose CCA (7)	Adult Female	NE [a]		0.220 [b]	0.114
MRID 48663505 Repeated Dose CCA (7)	PND 11 Male	2.232	1.786	NF	
MRID 48663505 Repeated Dose CCA (7)	PND 11 Female	4.567	1.079	NF	
MRID 48663501 RF Repeated Dose CCA (7)	Adult Male	NE [c]		NE [c]	
MRID 48663501 RF Repeated Dose CCA (7)	Adult Female	NE [c]		NE [c]	
MRID 48663501 RF Repeated Dose CCA (7)	PND 11 Male	NE [d]		NF	
MRID 48663501 RF Repeated Dose CCA (7)	PND 11 Female	5.142	3.521	0.332	0.266

[a] 10% inhibition was not observed
[b] Hill model allowed the best fit.
[c] n=2
[d] RBC ChE inhibition is more sensitive than brain ChE inhibition.
CCA = comparative cholinesterase assay
NDR = No dose response
NE = Not evaluated with BMD analysis
NF = no model fit
RF = Range finding

Appendix B. International Residue Limits

Diazinon (PC Code 057801; 10/23/15)

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US		Canada	Mexico[3]	Codex[4]
40 CFR 180.153 (a) General. Tolerances are established for residues of the insecticide diazinon, O,O-diethyl O-[6-methyl-2-(1-methylethyl)-4-pyrimidinyl]phosphorothioate (CAS No. 333-41-5)		O,O-diethyl O-[6-methyl-2-(1-methylethyl)-4-pyrimidinyl] phosphorothioate		Diazinon. The residue is fat soluble.
Commodity	Tolerance (ppm) /Maximum Residue Limit (mg/kg)			
	US	Canada	Mexico[3]	Codex[4]
Almond, hulls	3.0			5
Apple	0.50	.75		0.3 pome fruits
Apricot	0.20	.75		
Bean, lima	0.50	0.25 dry lima beans, succulent shelled lima beans		
Bean, snap, succulent	0.50	0.5 beans		0.2 common bean (pods and/or immature seeds)
Beet, garden, roots	0.75	0.75		
Beet, garden, tops	0.70			
Blueberry	0.50			
Caneberry subgroup 13-07A	0.75			0.1 Blackberries, boysenberry 0.2 raspberries, Red, Black
Carrot, roots	0.75	0.75		0.5
Cattle, fat	0.50			
Cherry, sweet	0.20	0.75		1 cherries
Cherry, tart	0.20			
Cranberry	0.50	0.25		0.2
Endive	0.70	0.75		
Fig	0.50	0.25		
Ginseng	0.75			
Grape[2]	0.75	0.75		
Hazelnut	0.50			
Kiwifruit[1]	0.75			0.2

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US		Canada	Mexico[3]	Codex[4]
Lettuce	0.70	0.75		0.5 lettuce, head and leaf
Melon	0.75	0.25 muskmelon, cantaloupes, watermelon		0.2 cantaloupe
Mushroom[2]	0.75			
Nectarine	0.20	0.7		
Onion, bulb	0.75	0.75 onions		0.05
Onion, green	0.75			1 spring onion
Pea, succulent	0.50			0.2 garden pea, shelled (succulent seeds)
Peach	0.20	0.7		0.2
Pear	0.50	0.75		0.3 pome fruits
Pineapple	0.50			0.1
Plum, prune, fresh	0.20	0.75		1 plums (including prunes) 2 prunes
Radish	0.50	0.25 roots		0.1
Rutabaga	0.75			
Spinach	0.70	0.75		0.5
Strawberry	0.50	0.75		0.1
Tomato	0.75	0.75		0.5
Vegetable, brassica, leafy, group 5	0.70	0.75 broccoli, cabbages, cauliflowers, kales kohlrabies, 0.5 Brussels sprouts, 0.25 collards		0.5 broccoli, cabbages head 0.05 Chinese cabbage (type pe-tsai), kale (including among others: collards, curly kale, Scotch kale, thousand- headed kale, not including marrow-stem kale) 0.2 kohlrabi
Watercress	0.05			
(c) *Tolerances with regional registrations*. Tolerances with regional registration, as defined in §180.1(l), are established for residues of the insecticide diazinon, *O*, *O*-diethyl *O*-[6-methyl-2-(1-methylethyl)-4-pyrimidinyl]-phosphorothioate (CAS No. 333-41-5)		Same as above		Same as above
Almond	0.50			0.05
Banana	0.20			
Celery	0.70	0.75		
Cucumber	0.75	0.5		0.1

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US		Canada	Mexico[3]	Codex[4]
Parsley, leaves	0.75	0.25		
Parsnip	0.50	0.25 roots		
Pepper	0.5	0.75		0.5 peppers Chili, dried 0.05 peppers, sweet (including pimento or pimiento)
Potato	0.10			0.01 (*)
Squash, summer	0.50	0.25		0.05
Squash, winter	0.75	0.25		
Sweet potato, roots	0.10			
Swiss chard	0.70	0.25		
Turnip, roots	0.50	0.5		
Turnip, tops	0.75	0.75		
MRLs With No US Equivalent				
Citrus fruits		0.7		
Hops (dried)		0.25		0.5
Salsify roots		0.75		
Wasabi		0.75		
Chicken eggs				0.02 (*)
Chicken meat				0.02 (*)
Chicken, edible offal of				0.02 (*)
Currants, Black, Red, white				0.2
Goat meat				2 (fat) V[5]
Kidney of cattle, goats, pigs and sheep				0.03 V[5]
Liver of cattle, goats, pigs and sheep				0.03 V[5]
Maize				0.02 (*)
Meat of cattle, pigs and sheep				2 (fat) V[5]
Milks				0.02 F[5]
Spices, fruits and Berries				0.1 (*)
Spices, roots, and rhizomes				0.5
Spices, seeds				5
Sugar beet				0.1
Sweet corn (corn-on-the-cob)				0.02
Walnuts				0.01 (*)
Completed by: M. Negussie; 10/30/15				

Summary of US and International Tolerances and Maximum Residue Limits			
Residue Definition:			
US	Canada	Mexico[3]	Codex[4]

[1]There are no domestic registrations for kiwifruit as of March 6, 2002.

[2]The expiration/revocation date for this tolerance is 9/10/2010.

[3] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

[4] * = absent at the limit of quantitation; Po = postharvest treatment, such as treatment of stored grains. PoP = processed postharvest treated commodity, such as processing of treated stored wheat. (fat) = to be measured on the fat portion of the sample. MRLs indicated as proposed have not been finalized by the CCPR and the CAC.

[5] V = The MRL accommodates external animal treatment

Appendix C. Tolerance Summary for Diazinon

Table C.1. Tolerance Summary for Diazinon (40 CFR §180.153).			
Commodity	Established Tolerance (ppm)	HED-Recommended Tolerance (ppm)	Comments
(a) General.			
Almond, hulls	3.0	3.0	
Apple	0.50	0.75	Harmonize with Canada MRL
Apricot	0.20	0.75	Harmonize with Canada MRL
Bean, lima	0.50	0.50	
Bean, snap, succulent	0.50	0.50	
Beet, garden, roots	0.75	0.75	
Beet, garden, tops	0.70	0.70	Beet, garden, leaves
Blueberry	0.50	0.50	
Caneberry subgroup 13-07A	0.75	0.75	
Carrot, roots	0.75	0.75	
Cattle, fat	0.50	0.50	
Cherry, sweet	0.20	1.0	Harmonize with Codex MRL
Cherry, tart	0.20	1.0	Harmonize with Codex MRL
Cranberry	0.50	0.50	
Endive	0.70	0.75	Harmonize with Canada MRL
Fig	0.50	0.50	
Ginseng	0.75	0.75	
Grape[2]	0.75	--	Revoke; tolerance expired 9/10/2010
Hazelnut	0.50	0.50	
Kiwifruit[1]	0.75	0.75	
Lettuce	0.70	0.75	Harmonize with Canada MRL
Melon	0.75	0.75	
Mushroom[2]	0.75	--	Revoke; tolerance expired 9/10/2010
Nectarine	0.20	0.70	Harmonize with Canada MRL
Onion, bulb	0.75	0.75	
Onion, green	0.75	0.75	
Pea, succulent	0.50	0.50	
Peach	0.20	0.20	
Pear	0.50	0.75	Harmonize with Canada MRL
Pineapple	0.50	0.50	
Plum, prune, fresh	0.20	1.0	Harmonize with Codex MRL
Radish	0.50	0.50	
Rutabaga	0.75	0.75	
Spinach	0.70	0.75	Harmonize with Canada MRL
Strawberry	0.50	0.75	Harmonize with Canada MRL
Tomato	0.75	0.75	

Table C.1. Tolerance Summary for Diazinon (40 CFR §180.153).			
Commodity	Established Tolerance (ppm)	HED-Recommended Tolerance (ppm)	Comments
Vegetable, brassica, leafy, group 5	0.70	0.75	Harmonize with Canada MRL
Watercress	0.05	0.05	
Almond	0.50	0.50	
Banana	0.20	0.20	
Celery	0.70	0.75	Harmonize with Canada MRL
Cucumber	0.75	0.75	
Parsley, leaves	0.75	0.75	
Parsnip	0.50	0.50	
Pepper	0.5	0.5	
Potato	0.10	0.10	
Squash, summer	0.50	0.50	
Squash, winter	0.75	0.75	
Sweet potato, roots	0.10	0.10	
Swiss chard	0.70	0.70	
Turnip, roots	0.50	0.50	
Turnip, tops	0.75	0.75	Turnip greens

Appendix D. Physical/Chemical Properties

TABLE D.1. Physical/chemical Properties of the Parent Compound Diazinon.	
Parameter	Value
Molecular Weight (g/mol)	304.3
Boiling point [a]	83 to 84°C
Melting point/range	Not Available
Specific gravity	Not Available
pH	Not Available
Vapor pressure (Torr, 25°C) [b]	7.22×10^{-5} 6.6×10^{-5}
Density	Not Available
Water solubility (20 °C) [a]	40 ppm
Solvent solubility [a]	acetone completely miscible benzene completely miscible dichloromethane completely miscible ethanol completely miscible 1-octanol completely miscible toluene completely miscible xylene completely miscible petroleum oils soluble
Dissociation constant, pKa	Not Available
Octanol/water partition coefficient, K_{OW} [b]	4898 (log K_{OW}=3.69) at 24°C 6393 (log K_{OW}=3.8) at 25°C
UV/visible absorption spectrum	Not Reported

[a] Reference: RD Memo, J. Morales, et. al., 8/23/2006; D329577.
[b] Reference: EFED Memo, K. White, 6/1/2016, D418979.

Appendix E. Summary of Directions for Use of Diazinon

Table E.1. Summary of Directions for Use of Diazinon.

Crop or Use Site	Registered Formulations	Equipment	Timing of application	Maximum Application Rate	REI Days
Almond	Soluble Emulsifiable Concentrate and wettable powder in Water Soluble Bags. EPA Reg. No. 19713-91, 19713-492, 61483-80 (impregnated formulation used in ear tags)	Chemigation, Airblast	Dormant	3.0 lb ai / a	7
Apple		Chemigation, Airblast	Dormant	2.0 lb ai / a or 0.02 lb ai/gal	4
			Foliar		
Apricot					
Beans, succulent		Chemigation, Groundboom	Preplant	4.0 lb ai / a	3
Beans, succulent (lima)					
Beets (greens) beets (root)					
Blackberry		Chemigation Airblast	At bud break	2.0 lb ai / a	5
			Delayed dormant	1.0 lb ai / a	
Blueberry Boysenberry		Chemigation Airblast		2.0 lb ai / a	
		Chemigation Airblast	Foliar	0.5 lb ai / a	
Broccoli		Chemigation, Groundboom	Preplant	4.0 lb ai / a	4
Cabbage		Chemigation, Groundboom	Preplant	4.0 lb ai / a	
Caneberries		Chemigation Airblast	At bud break, Delayed dormant	2.0 lb ai / a	5
Carrot		Chemigation, Groundboom	Preplant	4.0 lb ai/a	3
Cauliflower		Chemigation, Groundboom	Preplant	4.0 lb ai / a	4
Cherry		Chemigation Airblast	Delayed dormant through **foliar**	2.0 lb ai / a	
			Dormant	2.0 lb ai / a	
Collards		Chemigation, Groundboom	Preplant	4.0 lb ai / a	
		Soil drench	Preplant		
Cranberry		Chemigation, Groundboom	Foliar	3 lb ai / a	5
Cress, water		Chemigation, Groundboom	Crown	0.5 lb ai / a	4
		Soil drench treatment			
Cucumber (SLN)		Chemigation, Groundboom	Preplant	4.0 lb ai / a	3
Beef/range/feeder cattle (meat)		Animal treatment (ear tag)	When needed	.0264 lb ai / animal (max)	NS
Dewberry		Chemigation, Groundboom	At bud break	2.0 lb ai / a	5
		Crown and foliar treatment.	Before bud break	2.0 lb ai / a	
Endive (escarole)		Chemigation, Groundboom	Preplant	1.0 lb ai / a	4

Table E.1. Summary of Directions for Use of Diazinon.					
Fig		Chemigation., Airblast	Foliar.	0.5 lb ai / a	4
			Nursery stock	4.0 lb ai / a	NS
Filbert (hazelnut) Washington and Oregon only		Chemigation., Airblast	Foliar.	0.5 lb ai / a	18
			Nursery stock	4.0 lb ai / a	NS
Ginseng		Chemigation Groundboom	Pre-plant	0.5lb ai / a	3
Kale		Chemigation Groundboom	Preplant	4.0 lb ai / a	4
Lettuce, Lettuce, head, Lettuce, leaf (black seeded simpson, salad bowl, etc.)		Aerial, Chemigation, Groundboom	Preplant	2.0 lb ai / a	3
			Foliar	0.5 lb ai/ a	3
Loganberry		Chemigation Groundboom	At bud break.	2.0 lb ai / a	5
Melons, Cantaloupe, honeydew, Water melons,		Chemigation Groundboom	Preplant	0.8 lb ai / a	3
			Foliar	4.0lb ai / a	
			Nursery stock	4.0 lb ai / a	NS
Mustard		Chemigation. Groundboom	Preplant	4.0 lb ai / a	4
Nectarine		Chemigation Airblast	Dormant	2.0 lb ai / a	
		Chemigation airblast	Foliar	2.0.lb ai / a or 0.02 lb ai/gal	
			Nursery stock	4.0 lb ai / a	NS
Onion,, onions (green), onions (scallions), onions (spring)		Chemigation Groundboom	Preplant	4.0 lb ai / a	3
Ornamental and/or shade trees, Ornamental herbaceous plants Ornamental nonflowering plants Ornamental woody shrubs and vines		Groundboom, Hand held equipments	Nursery stock	1.0 lb ai/a or 0.01 lb ai/gal	NS
Parsley (SLN)		Soil incorporated	Preplant.	4.0lb ai / a	3
Peach		Chemigation airblast	Dormant.	2.0 lb ai / a or 0.02 lb ai/gal	4
			Postharvest.	1.0 lb ai / a	5
			Nursery stock.	4.0 lb ai / a	NS
Pear		Chemigation airblast	April.	2.0 lb ai / a or 0.02 lb ai/gal	4
			Foliar.	0.5 lb ai / a	
			Nursery stock.	4.0 lb ai/a	NS
Peas, succulent		Chemigation Groundboom	Preplant	4.0 lb ai / a	3
Pepper (SLN)			Preplant	4.0 lb ai / a	2

Table E.1. Summary of Directions for Use of Diazinon.					
		Chemigation Groundboom	Nursery stock		NS
		Soil incorporated	Preplant		2
Pepper (chili type) (SLN)		Soil broadcast			
Pineapple		Chemigation.	Foliar	1.0 lb ai / a	4
Plum		Chemigation airblast	Dormant	2.0 lb ai/A or 0.02 lb ai/gal	4
			Nursery stock	4.0 lb ai / a	NS
Potato, white/Irish (SLN)		Soil broadcast	Preplant	4.0 lb ai / a	3
Prune		Chemigation airblast	Dormant.	2.0 lb ai / a or 0.02 lb ai/gal	4
			Foliar	0.5 lb / a	
			Nursery stock	4.0lb ai / a	NS
Radish		Chemigation Groundboom	Preplant	4.0 lb / a	3
Raspberry (black, red)			At bud break	2.0 lb ai / a	5
			Delayed dormant	2.0 lb ai / a	
Rutabaga			Preplant	4.0 lb ai / a	4
Shallot			Preplant	4.0 lb ai / a	3
Spinach			Preplant	4.0 lb ai / a	3
Squash (all) (SLN)			Nursery stock	4.0 lb ai / a	NS
Strawberry			Foliar	1.0 lb ai / a	3
			Nursery stock	4.0 lb ai/ a	NS
Tomato			Preplant	4 lb ai / a	2
			Foliar	0.8 lb ai / a	
			Nursery stock	4.0 lb ai / a	NS

Appendix F. Residue Chemistry

Residue studies received since the last risk assessment; the summary and the regulatory implication of the study results (by crop).

Blueberry (MRID 46829401)
Six additional blueberry field trials were requested for the emusifiable concentrate (EC) and wettable powder (WP) formulations of diazinon. The six submitted field trials were performed using 1 lb ai/A of either the EC (Diazinon AG500) or WP (Diazinon 50W) formulation as a foliar application to blueberries with a 7 day pre-harvest interval (PHI). Current EC and WP label use allows up to 1 lb ai/A foliar application to blueberries with a 7 day PHI, which was reflected in the field trials. The study results showed that diazinon residues ranged from non-detectable (< 0.05 ppm) to 0.21 ppm for the EC applications and from non-detectable to 0.23 ppm for the WP applications.

The current 0.5 ppm tolerance for residues of diazinon on blueberries is adequate. HED concludes that the blueberry residue data deficiency cited in the 2004 IRED is now resolved.

Celery (MRID 45371214)
Five additional field trials using the diazinon 14% granular (14G) formulation on celery were requested. Three celery field trials were submitted with two treatment regimens per trial location. Trials were performed using 4 lb ai/A or 8 lb ai/A of the 14G on celery (preplant) with a 78-128 day PHI. Residues of diazinon in celery ranged from non-detectable (<0.01 ppm) to 0.04 ppm.

All granular uses of diazinon have been canceled (72FR40874; 12/6/2006). In addition, there are currently no registered uses of diazinon on celery for any formulation type. There is a current regional U.S. tolerance for diazinon on celery of 0.70 ppm. HED concludes that the celery residue data deficiency cited in the 2004 IRED is now resolved.

Spinach (MRIDs 45371204, 45371205, 46829402)
Five additional field trials on spinach were requested using a preplant application of the EC formulation followed by foliar applications of either the EC or WP. The subject spinach residue studies reflect the following: 1) five trials using a preplant application of the EC (4 lb ai/A) with 43-77 days PHI, or 2) five trials using a preplant application of the 14G (4 lb ai/A) followed by foliar application of the EC (5 x 0.5 lb ai/A=2.5 lb ai/A) with a 14 day PHI, or 3) five trials using a preplant application of the EC (4 lb ai/A) followed by foliar applications of the WP (5 x 0.5 lb ai/A=2.5 lb ai/A) with a 14-15 day PHI.

There are currently no registered granular formulations of diazinon. The current registered uses of diazinon on spinach include only preplant uses of the EC or WP at up to 4 lbs ai/A. The study reflecting current label rates for spinach (the preplant application of the EC formulation at 4 lb ai/A) showed non-detectable (< 0.05 ppm) residues. The current tolerance for residues of diazinon on spinach at 0.70 ppm is adequate. HED concludes that the spinach residue data deficiency cited in the 2004 IRED is now resolved.

Swiss chard (MRID 45371208)

Three additional Swiss chard field trials were requested reflecting preplant (14G and EC formulations) and foliar (WP and EC) applications of diazinon. Three Swiss chard field trials were submitted with two treatment regimens per trial location. The trials were performed using a preplant application of the 14G at 4.0 lb ai/A followed by foliar applications the WP (5 x 0.5 lb ai/A=2.5 lb ai/A) or using a preplant application of the EC at 4.0 lb ai/A followed by foliar applications of the EC (5 x 0.5 lb ai/A=2.5 lb ai/A), both with a zero day and 14 day PHI.

There are currently no registered granular formulations of diazinon. The study reflecting current maximum label rates for Swiss chard (the preplant application of the EC formulation at 4 lb ai/A followed by five foliar applications of 0.5 lb ai/A) showed non-detectable (<0.01 ppm) residues of diazinon at 14 days PHI. The current tolerance for residues of diazinon on Swiss chard at 0.70 ppm is adequate. HED concludes that the Swiss chard residue data deficiency cited in the 2004 IRED is now resolved.